Library of Congress Catalog
Card Number 59-10729

Printed in the United States of America

FOREWORD

This symposium of the American Association for the Advancement of Science, cosponsored by the American Medical Association's Committee on Cosmetics and the Society for Investigative Dermatology represents an endeavor of the Association to maintain close contact with developments in the basic biological sciences which have an ever increasing impact on the progress of medical sciences. The American Medical Association's ultimate aim is practical, namely to assure optimum medical care of the public. This aim is effectively promoted by the continued education of its physicians. However the Association is aware that success in education of its physicians and the improved care of the sick are inseparably connected with sound progress in the basic sciences because many of their results can be applied most successfully in medicine

This trend is expressed in the composition of the Committee on Cosmetics. Although the Committee deals with practical matters, it is composed of dermatologists and experimental pharmacologists who take active part in research in the field of cutaneous physiology The trend of research in dermatology makes this area particularly appropriate for a symposium From a medical science once devoted primarily to descriptive methods, it has progressed dramatically during recent years because of a change in emphasis A greater interest in its functional aspects has stimulated research on cutaneous physiology The application of these functional aspects in clinical dermatology has produced new ideas and knowledge that will improve patient care It is not sufficient that research be successful the news of this success must be disseminated. This is the purpose of this symposium

VERONICA LUCEY CONLEY
Secretary Committee on Cosmetics
American Medical Association

PREFACE

In the past, in textbooks of physiology that were arranged according to organs and organ systems, of all the chapters the one on physiology of the skin always was the leanest and emptiest. This poor showing was the result of the limited interest in the subject matter. Thus, scarcely any research was done in this field. Few facts were established. More or less the skin was regarded as a dead cover. Chapters on the skin were in sad contrast to chapters on subjects such as physiology of the kidneys, liver, musculature, respiration, gastrointestinal tract, and endocrine organs which were far advanced as early as the turn of the century. Part of the blame rested with the peculiar development of clinical dermatology. In all other fields physiology and clinical medicine exerted a mutually stimulating effect by setting common problems so that they could be approached experimentally, by exchange of methodological experiences, and by the fact that diseases often gave the first clue to clarification of physiological functions. In dermatology the main emphasis was on descriptive methods. Observation of morphological minutiae proved useful in establishing true disease entities, but thinking along functional lines developed slowly.

The situation has changed abruptly in the last twenty years with an unparalleled surge of interest in cutaneous physiology, an upswing which continues at an ever accelerating rate. More and more young investigators with broad basic training, the majority of them accomplished dermatologists, devote themselves with enthusiasm, imagination, and success to the study of cutaneous physiology and its applications in clinical dermatology. The exchange of knowledge and ideas among biologists and clinicians also has become a reality in this field.

This new direction of research is by no means neglecting or even opposing morphological observation and descriptive methods. Neither does it neglect clinical study or even forget the suffering patient, as some diehard dermatologists like to

claim On the contrary one of the main reasons for the great attainment of research in this field has been that function and structure have been correlated successfully more so than in any other area. Many examples of such fruitful correlation may be found throughout this volume clinical applications were emphasized everywhere

The invited speakers of this symposium have taken active part in the development just described In a two-day symposium it was impossible to include all phases of cutaneous physiology However the selection of subjects was not quite arbitrary An attempt was made to select topics that best illustrate the new development. It is hoped that this volume offers a fair illustration of what has been achieved by modern research in cutaneous physiology and pathophysiology

Students of the cutaneous system are greatly indebted to the American Association for the Advancement of Science for having arranged this symposium and to the Committee on Cosmetics of the American Medical Association and the Society for Investigative Dermatology for having sponsored it.

STEPHEN ROTHMAN

CONTRIBUTORS

IRVIN H. BLANK, Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts

ALAN C. BURTON, Department of Biophysics, University of Western Ontario, London, Ontario, Canada

ROBERT D. GRIESEMER, Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts

A. WESLEY HORTON, The Kettering Laboratory, Department of Preventive Medicine and Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio

ROBERT R. KIERLAND, Section of Dermatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

ALLAN L. LORINCZ, Section of Dermatology, Department of Medicine, University of Chicago, Chicago, Illinois

FREDERICK D. MALKINSON, Section of Dermatology, Department of Medicine, University of Chicago, Chicago, Illinois

HERMANN PINKUS, Departments of Dermatology, Wayne State University and College of Medicine and Receiving Hospital and the Detroit Institute of Cancer Research, Detroit, Michigan

RICHARD B. STOUGHTON, Section of Dermatology, Department of Medicine, Western Reserve University, Cleveland, Ohio

RAYMOND R. SUSKIND, The Kettering Laboratory, Department of Preventive Medicine and Industrial Health and Department of Dermatology, College of Medicine, University of Cincinnati, Cincinnati, Ohio

MARION B. SULZBERGER, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, New York University Bellevue Medical Center, New York

EUGENE J. VAN SCOTT, Dermatology Service, General Medicine Branch, National Cancer Institute, Bethesda, Maryland

BENJAMIN W. ZWEIFACH, Department of Pathology, New York University-Bellevue Medical Center, New York

CONTENTS

I THE INTEGUMENT AS AN ORGAN OF PROTECTION

II CIRCULATION AND VASCULAR REACTION

III SEBACEOUS GLAND SECRETION

IV PATHOGENETIC FACTORS IN PRE MALIGNANT CONDITIONS AND MALIGNANCIES OF THE SKIN

I The Integument as an Organ of Protection

RELATION OF THE ANATOMY OF NORMAL AND ABNORMAL SKIN TO ITS PROTECTIVE FUNCTION

RICHARD B STOUGHTON

Section of Dermatology Department of Medicine
Western Reserve University Cleveland Ohio

The primary function of skin is to protect its encased organism. Thousands of intricate biologic processes continually occurring in this unique organ are designed to perform this function. It is uniquely adapted to prevent injury from a multiplicity of noxious environmental influences. It is a magnificent barrier to water loss yet, when needed, it can provide excess water to the surface to maintain an even internal temperature It is an extremely efficient regenerative organ It manufactures, in the form of keratin one of the most flexible yet durable resistant structures known in nature It has created in form of melanin one of nature's most effective screens to ultraviolet light Its viable cells in the epidermis have developed physical attachments to each other which only the severest forces can disrupt. It has adapted intricate physical and chemical means to withstand successfully the continuous onslaught of innumerable microorganisms Many diseases of the skin are directly related to disturbances in its protective function

In this short presentation it will be possible to relate only a few of its more important and better understood protective functions.

Terminology

For purposes of orientation a few terms and structures will be defined The skin is divided into *dermis* and *epidermis* The following layers are recognized in the *epidermis*

The outermost layer of skin is a tough horny material called the *stratum corneum*

The process by which this layer is formed from viable epidermal cells beneath is known as the *cornification* process.

The proximal part of the stratum corneum is apparently a specialized structure with different properties from the horny material constituting the rest of the stratum corneum above. There is no official term for this area but because of its remarkable role in preventing absorption of agents through the skin it is now commonly called the *barrier area*

The cellular layer immediately beneath the stratum corneum is prominent because it contains unique basophilic granules and is called the *granular layer*

Below the granular layer lies the cellular epidermis. This consists of the *stratum Malpighii* and a layer of palisaded cells called the *stratum germinativum*

The area where epidermal cells meet the connective tissue is known as the *dermal-epidermal junction*

The connective tissue which along with its blood vessels and nerves is located between subcutaneous fat and epidermis and is known as the *dermis*

The specialized epithelial derivatives in the dermis such as sweat glands and ducts and the hair follicle with its attached sebaceous gland are frequently referred to as epidermal *appendages*

With apologies for a brief and inadequate coverage of terms and structures, I will now take up details of anatomy as they relate to the protective functions of skin.

Surface Film

The first line of defense of the skin against its environment is a thin film of emulsified material spread rather evenly over its entire surface. The components of this complex film are contributed by sebaceous glands, sweat glands, and the products of cornification. This even pliable film contributes to many essential functions among which are antisepsis, interference

with absorption of toxic agents, buffering of acid and alkali lubrication of horny layer and control of hydration of the horny layer The surface film contains innumerable products, many of which perform a known definite function.

Among the contents of the surface film are (a) lactic acid, amino acids urea, uric acid, and ammonia derived from sweat glands (b) triglycerides free fatty acids, and wax alcohols derived from sebaceous glands and (c) sterols, amino acids, pentoses, phospholipids, and complex polypeptides derived from the cornification process. The composition of this film will differ in different areas of the body and these differences will in many cases determine specific susceptibility of an area to a particular bacterium fungus or other parasites as well as determine regional localization of many common skin diseases. The soles of the feet, for example do not contain sebaceous glands and therefore do not contribute such products as triglycerides, fatty acids, and wax alcohols to the suface film of the sole of the foot. This is directly correlated with the facts (a) that fungus infections occur commonly on the soles of the feet and very rarely on the other parts of the lower leg and (b) that fatty acids derived from sebaceous glands are strongly fungistatic (1,2)

A simple example of a disease created by change in the surface film is that seen in the winter dryness of old people's skin which is technically known as asteatosis. The supply of lipid substances to the skin surface is insufficient so that the horny layer does not bind water properly becomes dehydrated scaly and fissured, with resultant extreme pruritus. If simple wool fat or petrolatum compounds are applied to the "dry" and scaling skin surface the process is rapidly brought under control so that the skin again appears supple and smooth and is no longer pruritic.

The scalps of children present friendly soil for the growth of epidemic ringworm fungi (microsporon audouini) whereas at the time of puberty these fungi can no longer grow in the scalp (2) Post pubertal scalps are rarely the site of infection by epidemic ringworm It is known that the concentration of fat substances

on the hair and scalp of children is lower than that of adults (3 4)

The surface film is well emulsified and spreads rapidly over the skin surface Sweat contributes a great deal to the emulsification and fluidity of the surface film (5)

Stratum Corneum

Proceeding from exterior to interior the next line of defense of the skin is represented by the horny layer This insensitive lining of tough fibrous material varies considerably in thickness over the body being thickest on the palms and soles and very thin in areas most protected from external trauma. It is a peculiarity of this layer that it increases in thickness in response to trauma (6) as well as being normally thicker even in utero in those areas (palms and soles) which bear or will bear the most trauma. The horny layer continually desquamates and is continually being replaced. These are features of the cornification process. The horny layer consists of countless tiny cells which have no nuclei and are desquamated as microscopic units from the surface What controls the process which binds and releases these adjacent cells is poorly understood However obvious clinical alterations in the horny layer such as calluses asteatosis ichthyosis and many other abnormalities are probably the result of malfunctioning of the mechanism binding and releasing these cells from each other

Selby's recent studies with the electron microscope show that the granular layer is the main site of final transformation of epidermal filaments into true keratin (7) The keratin cells lose their nuclei and become very compact but they maintain physical connections with neighboring cells through structures called desmosomes which are the same as the desmosomes or intercellular bridges of the lower cellular epidermis Selby speculates that the desmosomes may control separation of keratin cells from each other and thereby regulate desquamation The transformation of tonofibrils into true keratin probably involves molecular rearrangement as well as addition of amino

acids in which thiol-containing amino acids play an important part (8,9)

The cornification process is unique to the skin and some mucous membranes. However normal mucous membrane forms little or no true keratin When mucous membranes form true keratin they also develop a granular layer When this happens it is a pathologic change. It is well known that continuous trauma tobacco smoke and other insults will cause this change in mucous membranes. In many instances, this pathologic change in keratin formation is the forerunner of cancer

Poison ivy extracts applied to normal mucous membranes usually do not provoke any reaction even in a sensitized individual Lorincz has shown that the ivy extract does not serve as an antigen unless it is applied to skin which has the horny layer present (10)

The horny layer is a definite if not complete physical barrier to electromagnetic waves, microorganisms, parasites noxious chemicals, and practically all environmental agents. Its principal ingredient keratin is a tough fibrous protein which depends to a great extent on disulfide linkages and hydrogen bonds for its unique resistant properties (11) It is highly resistant to acid and alkali as well as common enzymatic proteolytic agents Because of the unquestioned importance of the horny layer in protection against the environment a brief review of the entire cornification process is warranted. A more detailed account is available in Rothman's text (12)

Starting in the basal layers of the cellular epidermis and extending to the top of the cellular epidermis there are numerous cytoplasmic filaments (tonofibrils) contained within all the cells (13 14) These filaments tend to agglomerate higher in the epidermis but remain quite constant in number (7) There are many reasons why these filaments may be regarded as forerunners of true keratin (*a*) keratin and epidermal cells have the same alpha type x ray diffraction pattern (15 16) (*b*) fibrous protein extracted from epidermal cells also has the alpha type x ray diffraction pattern and heat contraction response similar to keratin (17 18) (*c*) Selby has recently demonstrated by elec

tron microscopy that tonofibrils (filaments) are transformed directly into keratin in the granular layer (7) and (*d*) Stoughton has demonstrated that tonofibrils and intercellular bridges, like keratin probably contain more disulfide links and hydrogen bonds than the rest of the cytoplasm (19)

The final transformation of epidermal cells into keratin is *no doubt an active metabolic process which among other* things, involves loss of water release and uptake of amino acids, release of sterols and pentoses and apparent increase in activity of simple esterases (20) phosphatases (21) and β-glucuronidase (22)

It is extremely remarkable that peeling off only a few of the many layers of the stratum corneum results in an intense stimulation of mitoses in the stratum germinativum (23) Certainly one of the primary functions of the epidermis is to manufacture and maintain an intact layer of horny material between its host and the environment.

Barrier Area

Where the horny layer meets the granular layer there is a specialized area of keratin which seems to function as a selective and highly functional barrier to absorption This layer behaves as a lipid water sandwich (1) which means in part that substances having both water and fat solubility are more likely to pass through this area than are substances having primarily water or fat solubility It is equivalent to the stratum lucidum present on palm and sole and has electron microscopic properties which definitely differentiate it from the stratum corneum above and the stratum granulosum below (*7*) Very intense staining for sulfhydryl compounds can be demonstrated in this area by using the DNFB (dinitrofluorobenzene) method (25) The sulfhydryl groups present in this area differ from other sulfhydryl groups in that they (*a*) bind maleimide in such a way as to leave it free to combine with H acid (*b*) stain with DNFB much more intensely than with Bennet s reagent or the Barnett Seligman method and (*c*) are not differentiated by

tetrazolium (25) Other evidence indicates that sulfur-containing amino acids are utilized in keratin synthesis in this area (8,9).

The relation of any of the high thiol content of this area to its barrier like properties is not clear After damage or removal of the barrier area by stripping with Scotch tape the barrier to water loss and percutaneous absorption re-forms in from 24 to 60 hours (10,26) Once the barrier area is damaged or removed practically any molecule regardless of size or other characteristics will easily pass through the cellular epidermis.



FIG. 1 Palmar human skin. Stained with DNFB method. Barrier area is well outlined by intense stain.

Granular Layer

That the granular layer participates actively in keratinization can hardly be doubted, but details of its function are not known This layer disappears in many inflammatory and some malignant diseases. When this happens the horny layer retains

nuclear material. A metallic substance is definitely present in the keratohyalin granules, but its exact nature is unknown. However, it is known that copper catalyzes cornification (27) and it has been suggested that copper may be present in granular cells and perform this function (12). The work of Lansing and Opdyke, however, suggests that the metallic substance is calcium (28).

Cellular Epidermis

The cellular epidermis presents unique structural features which correlate well with its function as a protective organ. Electron microscopy has given us a better vision of the fine structures (7,13,14,29,30). Each epidermal cell contains innumerable tiny (50 angstroms) filaments believed to be fibrous protein. The main body of the cell consists of these filaments which are more condensed in the topmost cells than in the lower or basal cells. These filaments flow toward and terminate in dense linear areas on the cell membrane. The unique finding in epidermal cells is that each of these dense linear bands on the epidermal cell wall meets, directly, the identical process of a neighboring cell. However, there appears to be an amorphous material in a 300 A space between the opposing densities (7). The filaments do not run from one cell into another as previously thought by some (7,31), so that every epidermal cell is connected to its neighbor by a number of intercellular bridges. (Selby prefers to call these "desmosomes.") There is good evidence that these desmosomes are responsible for the integrity of the epidermis as a unit and that without them the cells would literally fall apart from each other and away from the body. This is precisely what happens, for example, in a fatal blistering skin disease known as pemphigus vulgaris. In this disease, microscopic analysis of the skin reveals fairly normal epidermal cells except for loss of intercellular bridges.

Blister formation is a basic reaction of skin to injury (32). There are many different types of blisters, but most of them involve the epidermis or the dermal-epidermal junction. Actually over thirty different skin diseases including the quite com

mon poison ivy dermatitis, involve the formation of blisters. Because of its importance as a basic reaction of skin to injury as well as a common pathologic event in disease processes blister formation will be discussed in more detail

Blistering diseases can be classified by microscopic morphology into five different types depending on whether (a) the separation is between the cellular epidermis and the stratum corneum or (b) the rete cells are stretched apart from each other but retain their long thin intercellular bridges and large

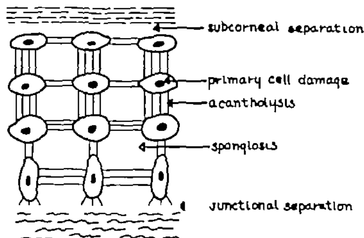


FIG. — Diagram showing different areas of blister formation in human skin disease Arrows indicate area of primary damage in blister formation.

spaces exist between the cells, or (c) the epidermal cells completely separate from each other and intercellular bridges are difficult or impossible to find or (d) separation of cells from each other is associated with severe damage to the interior of the cells (vesicant gas, heat or virus invasion) or (e) separation occurs between the cellular epidermis and the corium below

As stated above the fibrous protein of epidermal cells is similar in many respects to keratin We know that the integrity of keratin depends to a large extent on its disulfide links and hydrogen bonds. It is not too surprising then to find that disul

fide splitting agents such as thioglycollate, thioglycerol gluta thione and cysteine all break down intercellular bridges and cause the epidermal cells to separate from each other (19) Similar changes can be induced with 3–6 molar urea (19) and one assumes this to be due to its hydrogen bond breaking ac tivity particularly as the same results can be obtained with 75% lithium bromide also a hydrogen bond breaking agent



FIG. 3 Normal epidermal cells of human skin. The intercellular bridges are easily seen. 880×

(19) One is led to conclude from this that the connecting links between epidermal cells depend on disulfide links and hydrogen bonds and that the functional connecting links between epider mal cells are actually the intercellular bridges or desmosomes.

The epithelial lining cells of bowel trachea and esophagus have been shown to contain desmosomes just as epidermal cells do (33) This is of particular interest as it has been shown that these cells are also separated from each other by disulfide split

ting and hydrogen bond breaking agents (19 34) It seems that the physical and chemical devices for holding quite different types of epithelial cells together are similar

If epidermis is mildly injured with 50–60 C heat for 30 to 60 seconds and then incubated at 37 C either *in vivo* or *in vitro* the intercellular bridges disappear the cells fall apart

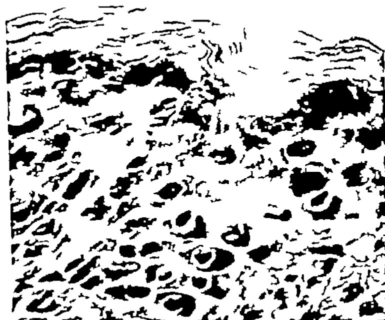


FIG. 4 Human skin treated with 3M urea for 10 minutes. Note loss of intercellular bridges and separation of cells from each other 780×

from each other and a blister forms (19,34) *In vitro* work with fresh human skin explants has shown that mild thermal injury releases enzymatic activity in the cell which results in break down of the intercellular bridges and subsequent separation of the cells (34) If the epidermal cells are exposed to freezing formalin suramin sodium Hg^{++} Ag^{+} or arsenate before the thermal damage and subsequent incubation neither the break down of intercellular bridges nor the separation of epidermal

cells from each other is observed (34) It appears then that the epidermis itself is quite capable of creating all the events necessary for blister *formation providing an initial physical injury* is supplied The enzymatic factor(s) present in epidermis, which cause the breakdown have not yet been identified Peptidases of many types have been isolated from whole skin (35–38) but Wells and Babcock have the only evidence for proteolytic



FIG 5 Normal human skin treated with thioglycollate 0 1M *pH 8.5 Note separation of cells and typ l acantholysis.*

enzymes in the epidermis (39) It is not even determined what class of enzymes is responsible for the blister process following thermal injury An enzyme has been identified in extracts of *stool from patients* with ulcerative colitis which will break down intercellular bridges in formalin fixed epidermal cells (40) This enzymatic activity is different from the well known proteolytic or mucolytic enzymes and seems to be present only in stools from patients with ulcerative colitis. Cantharidin will

break the intercellular bridges and give blister formation in this way It has been shown that cantharidin will do the same thing in fresh skin removed from the body and incubated at 37 C (41) Agents which when applied to the skin cause blister formation in almost anyone are classed as primary irritants It is quite likely that different primary irritants have different mechanisms of action Blister formation resulting from separa

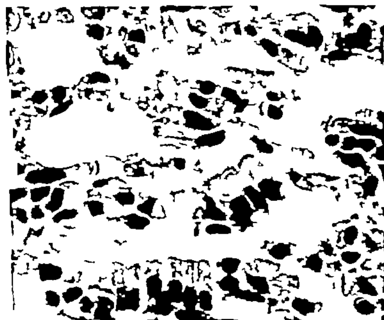


FIG. 6. Normal human large bowel exposed to 3M urea for 10 minutes. Note clean separation of bowel epithelial cells. 680×

tion at the dermal-epidermal junction will be discussed under the latter heading

Many loose statements concerning blisters resulting from hydrostatic pressure have found their way into the texts Experimentally if fluid is injected directly into the epidermis or corium under maximal manual pressure it is impossible to create *in vivo* a blister in human skin This should suffice to rule out hydrostatic forces as the primary cause of blister for

mation under pathophysiologic conditions. Also, it is almost impossible to create a true blister by shearing action or direct friction on skin. The blisters resulting from friction are secondary to damage of the cell and follow the initial injury by a sizable time interval. Pictures shown of blister formation following directly a severe frictional force (47) cannot be distinguished from that seen directly following severe heat application (43,44).

One last important consideration in blister formation is the



FIG. 7. Section of skin from patient with pemphigus ... Note the separation of epithelial cells from each other which allows the blistering in this disease. Compare this picture to the separation of epithelial cells induced by heat (Fig. 8), thioglycollate (Fig. 5), urea (Fig. 4), and with normal skin (Fig. 3). 480 ×

osmotic pressure of the epidermal intercellular fluid. This is unknown, but one can speculate that breakdown products (proteolysis?) of the epidermal fibrous protein increase osmotic pressures, attract fluid, and give rise to the typical tense ele

vated blister Also breakdown products of the epidermal structures could act as leukotaxins in the corium directly beneath (45) Recent work indicates that breakdown products of the epidermis following thermal injury act as rather specific attracting forces for eosinophils which accumulate in large numbers around vessels wherever the epidermal extract is injected in human skin (46)

Thickening of the cellular epidermis is known as acanthosis and thickening of the horny layer is known as hyperkeratosis. Acanthosis is observed with a wide variety of diseases, but only a small percentage of the population will respond to chronic trauma with acanthosis. When subjects are exposed for long periods to an automatic scratching machine at regular intervals some will react to this with acanthosis and others will not (47) Another study indicates that all people respond to chronic rubbing of the skin with an increase in the thickness of the horny layer or hyperkeratosis (6) Exposure to ultraviolet light will also increase the thickness of the horny layer (48)

Melanin Pigment

One of the primary functions of melanin pigment in skin is to protect the organism from ultraviolet light. When melanin is absent from skin as in vitiligo or albinism the skin can tolerate only the smallest amounts of ultraviolet light without a severe reaction In normal skin exposure to ultraviolet light results in darkening of preexisting melanin as well as formation of new melanin (49,50) It is also quite well established that melanin by its screening of ultraviolet light protects the skin against development of the common epidermal malignancies (51) The only cells in the human body capable of forming melanin are derived from the neural crest and are present primarily in skin and eye but may also be found in the leptomeninges. Their unique feature is the ability to convert tyrosine to dihydroxyphenylalanine by an enzymatic process involving tyrosinase Congenital absence of the enzyme tyrosinase results in albinism. In vitiligo, an acquired loss of pig

ment in the skin the melanocytes are present, but for reasons unknown they no longer form melanin pigment The number of melanocytes in different races is about the same the main difference being in the amount of pigment in each cell

A number of compounds natural and synthetic, when present in skin will cause severe erythema and blistering of skin when



FIG. 8 Normal human sk n exposed to 55 C for 90 second and then incubated at 37 C for 12 hours Note ad nced epithelial c ll separation 655×

exposed to ultraviolet light (59,53) This reaction even in its minimal form results in dense hyperpigmentati n of the skin *There are also a few compounds which* when applied to skin will decrease or completely inhibit the formation of pigment (54) Some of these compounds are utilized though rather unsuccessfully to regulate the amount of pigment in human skin

It is well known that heavily pigmented skin is more re-

sistant to external irritants. It is also known that melanin is capable of crosslinking with protein to form a tough resistant compound (55) This may help to explain the generally accepted observation of the superior resistance of heavily pigmented skin to irritants.

Dermal Epidermal Junction

The area of contact between epidermis and corium is a specialized one in many respects. Electron microscopy shows that there is a definite membrane in this area which is separated from the wall of the basal cell above by a submicroscopic space (13) Histochemistry also reveals a dense accumulation of polysaccharide material at the dermal-epidermal junction (56)

In spite of prolonged previous controversy about the existence of a definite basement membrane, it appears now that a membrane like structure does exist. Its functional role no doubt concerns the cementing of epidermis to the corium below Even excessive shearing forces will not separate the epidermis from corium in normal skin Excessive hydrostatic pressure exerted *in vivo* by forceful injection of fluid into the corium will not cause separation of the epidermis from the corium. There are however a number of blistering diseases of skin in which the primary pathology is separation of the epidermis from the corium (52) Experimentally the epidermis may be easily separated from the corium after heating the skin to 50 C (57) The epidermis will readhere to the corium below after the skin is allowed to cool Felsher was able to separate the epidermis from corium by exposing skin to ions and pH which are known to cause collagen swelling (58) Collagenase will degrade the polysaccharide membrane of formalin-fixed skin whereas trypsin hyaluronidase and other mucolytic and proteolytic enzymes will not (59) In fresh specimens many proteolytic and mucolytic enzymes will cause separation of epidermis from corium (60)

It seems logical that the epidermis is cemented to the corium at least in part, by a gel state of polysaccharide material at the

junction Percival has shown that dye injected into the corium spreads diffusely through the corium but will not penetrate the junctional area (61) It is doubtful that the junctional area presents any significant barrier to absorption of materials from epidermis through to the corium The role of the junctional area in preventing invasion of organisms has not been adequately investigated. That organisms can and do pass through the junctional area is obvious, but the fact that they do so only rarely leads one to suspect some barrier to organisms in this area.

Sweat Glands

Man s protection against a warm environment is primarily his ability to sweat and change peripheral blood flow Circulation will be discussed by others, leaving us to deal with the organ for sweating. It is simplest to consider three parts of the eccrine sweat unit (*a*) the glandular part deep in the dermis which is responsible for secreting sweat (*b*) the dermal portion of the duct which transports sweat and (*c*) the epidermal portion of the duct which delivers sweat to the surface of the skin The sweat mechanism in man may deliver up to 14 liters of sweat per day Excess demand on the sweat gland may result in severe damage to the eccrine secreting cell (C9) The secretory pressure of sweat may be as high as 210 mm Hg Whether this is pure secretory pressure or that plus contraction of the myoepithelia of the duct and/or electroosmotic forces (5) is not known. The epidermal portion of the duct contains a prominent inner lining of dense homogeneous material which is not glycogen although it stains with the periodic acid Schiff technique (63 64) This lining also stains intensely for disulfide compounds. It is quite likely that the lining membrane may be involved in the common reaction called miliaria or prickly heat In this condition the epidermal sweat duct is blocked sweat backs up in the duct leaks out into the epidermis or corium and causes an inflammatory reaction Sweat duct occlusion occurs in a persistent hot humid environment and may be caused experimentally by a number of seemingly different

methods (65 66) The most serious result of sweat duct occlusion is a systemic reaction of hyperthermia hyperventilation malaise and *total incapacitation which occurs* when a large number of sweat ducts are blocked and the individual remains in a hot environment. This was a severe problem in military personnel in the South Pacific during World War II (5) The epidermal sweat duct functions as a completely independent unit which does not participate in numerous inflammatory and malignant diseases which may involve surrounding epidermal cells. Also if the epidermal sweat duct unit is severed it will replace itself rapidly in a spiraling proliferation of cells completely oblivious of the presence or absence of surrounding epidermal cells (67)

Sweat glands are innervated by sympathetic fibers, but pharmacologically these fibers are cholinergic. Cholinesterase can be demonstrated histochemically in large amounts around the eccrine sweat glands (68)

REFERENCES

1 Peck, S M Rosenfeld, H Leifer W and Bierman, W *Arch Dermatol and Syphilol 39* 126 (1939)
2 Rothman, S., Smiljanic, A and Weitkamp A. W *Science 104* 201 (1946).
3 Rothman, S., Smiljanic A and Shapiro, A. *Proc Soc Exptl. Biol. Med. 60* 394 (1945).
4 Rothman, S., Smiljanic A and Shapiro, A. L. *J Invest. Dermatol. 8* 81 (1947)
5. Sulzberger M B., and Herrmann, F *The Chemical Significance of Disturbances in the Delivery of Sweat* C. C Thomas, Springfield, Ill 1954
6. Rubin L. *J Invest Dermatol. 13* 313 (1949)
7 Selby C. C. *J Invest Dermat l 29* 131 (1957)
8. Bern, H A. *Nature 1 4* 509 (1954).
9 Ryder M L. *The Biology of Hai Growth* W Montagna and R. A. Ellis, Ed tors. Academic Press, New York and London 1958. Page 305
10 Loriner A L. *J Invest Dermatol 28* 275 (1957).
11 Alexander P and Hudson, R. F *Wool—Its Chemistry and Physics* Reinhold Publishing Corporation New York, 1951
12 Rothman, S. *Physiology and Biochemistry of Skin* University of Chicago Press, Chicago Ill 1954.

13 Selby C. C. *J Biopl ys Biochem Cytol 1* 4?9 (1955)
14 Odland, C Presented before the Society of Investigative Dermatology New York June 1 19.7
15 Giroud A and Champetier C. *Bull s c cl im biol 18* 656 (1936)
16 Derksen J C. Heringa C C., and Weidinger A. *Acta Neerl Morpl ol 1* 31 (1937)
17 Rudall, K M Symposium on *Fibrous Protein The Structure of Epidermal Protein* Society of Dyers and Colourists, 15 1956
18 Roe, D A *J Invest Dermatol* , 1 (1956)
19 Stoughton R B *J Invest Dermatol* 7 393 (1956).
20 Montagna W *J Bioplrys Biocl em Cytol 1* 13 (1955)
21 Fisher I and Glick, D *Proc Soc Exptl Biol Med 66* 14 (191)
22. Seligman, A. M Tsou, Kwan-Chung, Rutenburg, S H and Cohen, R B *J Histocl em Cytocl em 2* ?09 (1954)
23 Pinkus H *J Invest Dermatol 16* 383 (1951).
24 Treherne J E *J Plrysiol (London) 133* 171 (1956)
25 Burstone, M S *J H stocl em Cytocl em 3* 3? (1955).
25a Stoughton R B Unpublished results.
26 M lkinson F I resented before Academy of Dermatology and Syphilology Ch cago, Ill December 10 1957
27 Marston H R. In *F brou Proteins.* Proceedings of a symposium held t the University of Leeds May 1946 Society of Dyers and Colourists, Bradford, England 1946 Page 207
28 Lansing, A I and Opdyke D *Anat Reco d 10* 379 (1950)
29 Pease D C. *Am J Anat* 89 169 (1951)
30 Laden, E L., Erickson, J O nd Armen D *J Invest Derm tol 19* 11 (195)
31 Porter K R *An t Rec d 118* 433 (1954).
32 Stoughton R B *A M A A cl Dermatol* 6 581 (1957)
33 Fawcett D Cited by Selby in reference 7
34 Stoughton R B and Novak N *J In est Dermatol* 6 197 (1955)
35 Beloff A and Peters R A *J Phy ol (London) 103* 461 (1945)
36. Fruton J S *J Bi l Chem 166* ?1 (1946)
37 Martin, C. J and Axelrod, A E. *J Biol. Chem 21* 309 (19 7)
38 Zamenck P C Stephenson, M C and Cope O *J Biol Cl em 158* 135 (1945)
39 Wells, C C., and Babcock C. *J Invest Dermatol 1* 159 (1953)
40. Stoughton R B. *Sc ence 116* 37 (195).
41 Epstein W Personal communication

4_ Naylor P F *Brit J Dermatol* 67 397 (1955)
43 Leach E. A Peters, R. A., and Rossiter R. J *Quart J Exptl Physiol* 32 67 (1913)
44 Personal observations.
45 Cullumbine, A., and Rydon A. N *Brit J Exptl Pathol* ?7 341 (1955).
46. Stoughton, R. B. Unpublished results.
47 Goldblum, R. W., and Piper W N *J Invest Dermatol.*, 22 405 (1954).
48. Miescher G *Stral lentherapie* 35 403 (1930)
49 Miescher G and Minder H. *Strahlentherapie* 66 6 (1939).
50 Edwards, E., and Duntley S Q *Am J Anat* 65 1 (1939)
51 Pillsbury D Shelley W and Kligman, A. *Dermatology* W B. Saunders Co Ph ladelphia, Pa., 1956
52. Lerner A. B Denton, C. R. and Fitzpatrick, T B *J Invest Dermatol* 20 299 (1953)
53 Blum H F *Physiol. Revs.* 25 483 (1945)
54 Schwartz, L., Warren, L. H and Oliver E. A *Weekly Pub Health Rept.*, 55 1111 (1940)
55 Stary Z. *Bull fac méd. (Istanbul)*, 1 528 (1949).
56. Stoughton R. B and Wells G C. *J Invest. Dermatol* 14 37 (1950)
57 Baumberger J P Suntzeff V and Cowdry E. V *J Natl Cancer Inst* 2 413 (1942)
58. Felsher Z. *J Invest Dermatol.*, 8 35 (1947)
59 Stoughton R. B and Lorincz A. L. *J Invest Dermatol.*, 16 43 (1951)
60 Hambrick, G and Blank H *J Invest Dermatol* 23 437 (1954).
61 Percival, G H and Hannoy R. W *Brit J Dermatol. Syphilis* 61 41 77 (1949).
6_ Dobson, R. L., Formisano V Lobitz, W., and Brophy D J Invest Derm tol., 31 147 (1958).
63. Cormia F E and Kuyendall, V *A.M.A Arch Dermatol* 71 425 (1955)
64. Hambrick, G *J Invest Dermatol.* 29 213 (1957).
65. Shelley W B. and Horvath, P N *J Invest Dermatol* 14·9 (1950).
66 Shelley W B and Horvath P N *J Invest Dermatol* 14 193 (1950).
67 Lobitz, W C., Jr Holyoke J B., and Montagna, W *J Invest. Dermat l.* 22 157 (1954)
68 Hurley H Shelley W nd Koelle G *J Invest Dermatol.*, 21 139 (1953).

DISCUSSION

DR. BYTHEWOOD (Presbyterian Hospital, Newark, N J) From your remarks, particularly about enzymatic action do you think cold applications are of therapeutic value in thermal injuries?

DR. STOUGHTON Theory tells us they would be of value, but I don t know of experimental proof

DR. SULZBERGER Is the barrier thinner or does it disappear in the hair follicle at about the level of the opening of the sebaceous gland duct? It is at this point that Franz Herrmann and our group found that substances penetrate into the skin most readily

DR. STOUGHTON I don t have exact information on this point. It is hard to quantitate the morphologic features of the barrier

PROTECTION AGAINST THE TRANSFER OF MATTER THROUGH THE SKIN

ROBERT D GRIESEMER

Department of Dermatology Harvard Medical School
Massachusetts General Hospital Boston Massachusetts

The chief function of the integument, protection is largely dependent upon special structural features of the epidermis. The toughness of the entire external horny layer the stratum corneum makes the epidermis resistant to many kinds of physical and chemical agents. The failure of physical agents to penetrate through the stratum corneum is diagrammatically shown in Fig 1 The effect of trauma and large particles is cushioned by the resilience of the dermis and fatty tissue which underlie the epidermis. The tough fibrous protein keratin in the stratum corneum withstands direct shearing and friction The closely knit keratin mesh within the cells of the horny layer and the tightly packed arrangement of these cells prevent movement of all but the smallest molecules through the intact epidermis.

Chemical agents of small molecular dimensions probably pass directly through the epidermis of intact skin (Fig 2) Penetration through the superficial stratum corneum is rapid but at the base of the horny layer it is enormously retarded by the main barrier Passage from the barrier to the capillary bed is rapid with possibly a little retardation at the junction between epidermis and dermis.

Chemical substances whose penetration is blocked by the barrier may be held by the stratum corneum. The physiological process of continuous shedding of the stratum corneum casts off these adsorbed substances which eventually might penetrate.

If the barrier layer is fractured both physical and chemical agents can penetrate all layers of the skin very rapidly (Fig 3) Even the smallest scratch increases the permeability to liquids and dissolved substances Larger breaks obviously permit all physical and chemical agents to enter the body without restriction Rapid repair of such breaks, which closes the portal of entry of large molecules, is an important part of the protective function of the skin.

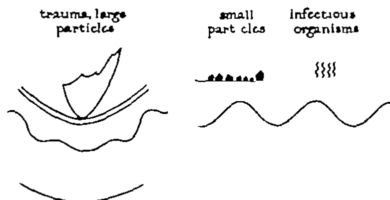


Fig. 1 Intact sk n resists the effect of physical agents such as trauma and the penetration of particles and microorgani ms.

Avenues of Penetration of Chemical Substances

Chemical substances may pass through the epidermis into the dermis in three ways (*a*) through patent hair follicles into sebaceous glands (*b*) through the spiral sweat ducts and (*c*) directly through the epidermis Since epidermis extends beyond the mouth of the sebaceous duct within the hair follicle it is possible that the course of transfollicular penetration is mainly transepidermal All three avenues may take part in the transfer of a chemical substance Witten (1) interpreted his auto radiographic studies with thorium X to indicate that this substance penetrated to the dermis by all three routes. However specific substances may prefer one avenue to the other two In 1915 Rothman pointed out that lipid-soluble substances probably

enter mainly through the sebaceous glands (2) In 1956 Mali (3) published data which he thinks indicate a dominant role for the sweat duct in the in vivo passage of water out of nonsweating skin. Blank Griesemer and Gould (4) have published autoradiograms of rabbit skin which had been exposed to the anticholinesterase sarin tagged with P^{32} These indicate that penetration occurred through the epidermis itself and not preferentially through the hair follicles. A similar route of penetration through epidermis and not via hair follicles was described for C^{14} hydrocortisone by Scott and Kalz (5)

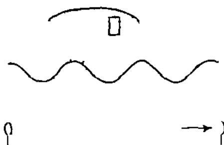


Fig. 2 Intact skin allows penetration of chemical agents of low molecular weight. The rate of penetration is markedly decreased by a thin barrier layer at the base of the stratum corneum From the barrier to the capillary bed, chemical agents diffuse freely The small rectangular area is shown in higher magnification in Fig 5

The problem of avenue of penetration has not been solved. A series of autoradiograms taken at various time intervals should demonstrate the route of entry of a radiotagged substance into the skin. Adequate studies of this kind have not yet been reported Unless future studies prove otherwise the main avenue of transfer of many chemical agents across intact skin may be considered to be a path directly through the epidermis.

Barrier Layer in Epidermis

In 1924 Rein (6) demonstrated, at the junction between the horny layer and the granular layer underlying it, an electro-

negatively charged barrier which repelled anions and attracted and held cations from further penetration Rothman (7) in 1929 felt that this charged layer checked the transfer of water across skin *Blank* (8) in 1953 showed graphically that the barrier to water transfer in skin is a layer a few microns thick at the base of the stratum corneum He used the adhesive tape stripping method of Wolf (9) and Pinkus (10) to remove the stratum corneum gradually He found that the diffusion of water through skin remained low until the base of the stratum

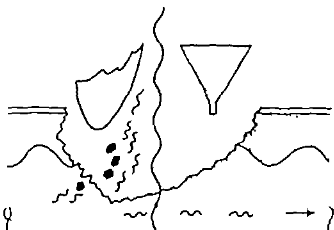


Fig 3 When the barrier is disrupted, all physical and chemical agents pass unimpeded into the epidermis and dermis.

corneum had been stripped away thereafter the permeability to water rose sharply Szakall (11) reported in 1951 that after the stratum corneum had been stripped off with tape the entire barrier could be removed on Tesa tape in a single stripping Subsequently he recovered the barrier layer by dissolving the tape in petroleum ether Mali isolated the barrier by another method in 1955 (3) After maceration of skin for two days in 1 per cent methylene blue solution he scraped away the stained stratum corneum and rete layer leaving the unstained barrier intact.

The effectiveness of the barrier has been further demon-



FIG. 4 (*Left*) Autoradiogram of 10 sections of intact human skin to which sarin tagged with P^{32} had been applied for 30 minutes. Tissue was absent at time of photography (1.5×). Epidermis on top. Essentially no penetration into the dermis can be detected. (*Center*) Autoradiogram of 6 sections of slightly scratched human skin to which radioactive sarin had been applied for 30 minutes. Tissue was absent at time of photography (1.5×). Epidermis on top. The dark shadows indicate rapid penetration of sarin into the dermis through the site of the scratch. (*Right*) Photomicrogram of one of the sections of scratched skin used for the autoradiogram in Fig. 4 center. Radiosensitive emulsion was absent at time of photography (125×) hematoxylin and eosin. The scratch has extended through the barrier into the living epidermis.

strated by the increased ease of penetration of radioactive sarin after slight scratching of the skin (Fig 4) This work demonstrates the necessity in permeability studies of regarding as normal only skin in which the barrier remains uninjured.

A simple method has been devised for rapid determination of whether or not the barrier is intact (12) The electrical conductivity of the skin is measured by means of the simple circuit described by Levine in 1933 (13) The electrical conductivity of excised human skin and its permeability to sarin have been shown to parallel the degree of damage resulting from stripping (see Table I) Only in skin of low conductivity is the barrier intact.

TABLE I The effect of serial stripping with adhesive tape on the electrical conductivity and permeability to sarin of excised human skin

Degree of *injury*	*Conductivity* μ*amp*	Penetration of sarin $m\mu M/cm^2$ *hr*
Control	1	[illegible]00
6 strippings	17	429
12 strippings	17	436
1 stripp ngs	65	47[illegible]0

The rate of repair of the barrier can be followed by periodic measurement of the conductivity of injured sites. Griesemer has found that superficial scratches heal within 24 to 48 hours (14) Thus, part of the skin's protective function depends on rapid reconstruction of the barrier

Direct Penetration of the Epidermis

Perusal of the literature on the permeability of intact skin reveals a dearth of thoughtful investigations on both the pathways and the physicochemical mechanisms by which chemical agents penetrate through the skin The excellent reviews of this subject by Lang (15) Rothman (16) and Malkinson (17) show all too clearly that only a very few investigators have been concerned with more than superficial demonstration of the fact that sub-

stances diffuse through skin. Rates of permeability have rarely been determined. The thoughtful discussions of skin permeability published by Higuchi (18), Guillet (19), and Treherne (20) are significant contributions to knowledge in this field. To attain a more profound understanding of permeability of the skin, a clearer understanding is needed of (a) the structures which penetrating molecules are likely to encounter in their direct passage through the epidermis and (b) the physical and chemical factors which affect transepidermal diffusion of these molecules.

ANATOMY

When placed on the surface of the integument, a penetrating substance first comes into contact, not with the skin itself, but with a surface film composed of sebum, sweat and its residue and desquamating stratum corneum. The chemical composition of this film is complex and variable. The character and extent of its interaction with a penetrating agent are exceedingly difficult, if not impossible, to predict. They will vary with the physical state of the penetrating agent—whether it be solid, liquid, or gas—and, if the agent is in solution, with the nature of its solvent. Once the penetrating agent has passed through this surface film to the skin itself, the sebum, sweat, and other substances of which the film is composed probably have very little effect on the subsequent pathways and mechanisms by which the agent penetrates into or through cutaneous tissue.

Figure 5 shows diagrammatically the histological structures encountered by a substance as it penetrates through the stratum corneum to the stratum granulosum. The barrier which limits penetration lies between these two layers. Above and below the barrier, penetration takes place freely. In the superficial stratum corneum, a penetrating molecule is most likely to pass through the air-filled or moisture-lined intercellular spaces where it would encounter essentially no resistance. Some molecules might pass directly through the cells of the stratum corneum, but penetration by this route would be much slower

In the barrier where intercellular spaces are narrower and cells are denser resistance to diffusion increases. A molecule which passes this bottleneck can again diffuse without great resistance through the liquid within the intercellular spaces of the stratum granulosum and lower living epidermis to the

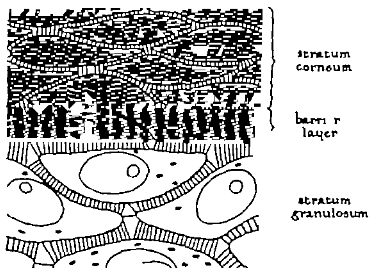


FIG. 5 Magnification of rectangle in Fig 2. The cells of the barrier are more compact and more closely bound together than are those of the stratum corneum The intercellular spaces are smallest in the barrier and largest in the living epidermis beneath. In the stratum corneum, the intercellular spaces increase in size as the cells separate and fall away into the external environment. The small rectangular area in the barrier is shown in higher magnification in Fig 6.

dermis and finally to the capillaries, whence it is distributed throughout the organism.

Selby has used the electron microscope for study of the detailed structure of the epidermis in the region of the barrier (91) Figure 6 is a diagrammatic representation of the microanatomy of cellular junctions as they appear in her photographs of this area. In the center of each intercellular bridge (desmosome) a narrow space separates the cell membranes. This space contains some electron density In the living epidermis it is 300 A

wide in the barrier only 900 A. In other words, the cells of the barrier appear to be more closely bound to each other than do those of the living epidermis Nevertheless in Selby's microphotographs there is intercellular space between adjacent desmosomes which could serve as a wide avenue of penetration for molecules. The question arises of whether this space which appears in the electron microscope picture actually exists as



FIG. 6. Diagram of cellular junction in barrier layer taken from electron microscopic photograph in Fig 11 of Selby's paper (21) Desmosomes, or intercellular bridges are not continuous from cell to cell well-defined cell membranes cross the center of each bridge. Between adjacent desmosomes the cell membranes have retracted, leaving intercellular spaces. These spaces have no electron density they may be artefacts, electron-dense material present in life may have been lost during preparation of tissue for electron microscopy

such *in vivo* or is merely an artefact. If the space does exist during life what does it contain? One must consider the possibilities that molecules might penetrate the barrier through this space or through the cells which form the barrier or through both the space and the cells.

PHYSICOCHEMICAL FACTORS

Biochemistry

The material within the intercellular spaces of the epidermis is derived from the adjacent epidermal cells themselves and

from fluids circulating slowly from the dermis. Its composition is not precisely known but probably includes lipid carbohydrate and protein substances The arrangement of these substances within the intercellular spaces is even less well understood than their composition One can only speculate whether they are loosely organized into some fibrous structure in a gel state or into a well-defined lipid-protein barrier similar to plasma membranes.

While there is no direct evidence about the chemical and physical structure of the intercellular material histochemical data concerning the entire barrier layer have been obtained by Stoughton (99) and the biochemical composition of human stratum corneum and living epidermis has been determined by Matoltsy (23 24) In Stoughton s work as in the anatomical studies already mentioned there is evidence that the barrier may be denser than the rest of the stratum corneum Stoughton demonstrated that its reaction to stains differs from that of the rest of the stratum corneum This difference is subtle and would be difficult to detect by Matoltsy s biochemical methods until they had been adapted for use on a microscale Matoltsy found that the relative proportions of components in the stratum corneum was roughly the same as in the living epidermis, namely keratin 75 per cent lipid 8 per cent carbohydrate 9 per cent indestructible cell membranes 5 per cent and soluble dialyzable substances of low molecular weight 10 per cent Examination in polarized light showed intense positive double refraction parallel to the skin surface not only in the barrier but also in the rest of the stratum corneum This indicates a tight packing of fibrous elements parallel to the long axis of the horny layer cells. Probably some lipid is interspersed between these elements It would be interesting to apply Matoltsy s methods to the barrier after it had been isolated by the techniques of Mali (5) and Szakall (11)

It is hard to imagine that molecules would penetrate the cells of the barrier more easily than the material in the intercellular spaces which should be less dense and less organized than the

cells. One cannot be certain of actual conditions, however without more information than we now have. Permeability studies alone cannot determine whether the molecular pathways in the epidermal barrier lie in the intercellular spaces in the cells themselves, or in both. Permeability studies may be expected to reveal only the chemical structure of the linings of molecular pathways and not their anatomical location. Investigation of the effect of solvents on the permeability of the barrier followed by electron microscope and histochemical study of the altered barrier might provide definitive evidence.

Physical Chemistry

From studies of diffusion in simple physical systems and through simple biological membranes such as that of the red blood cell physical chemists and biophysicists have discovered the principles of permeation in various kinds of membranes. These can be expressed in mathematical form and are beautifully discussed by Davson and Danielli (25) and by Higuchi (18). The degree of molecular interaction between a penetrating substance and a membrane determines the nature of the permeation mechanism. Most of the properties which affect permeability—partition coefficient, viscosity charge Q_s—are derived from the interaction between forces which attract one molecule to another. The strength of interaction varies from the weak van der Waals force between $-CH_2$ groups to the strong electrostatic force between ions. Molecular volume also plays a role in permeability when the dimensions of pathways in a membrane approach those of penetrating molecules, but this state of affairs is rarely seen in biological membranes.

The partition coefficient of a penetrating substance between its vehicle and a membrane and between a membrane and its receptor solution has a large effect on permeability. It depends chiefly on the force of molecular interaction between membrane and penetrating molecule. Polar substances have low affinity for nonpolar membranes. Highly polar membranes reject nonpolar molecules but attract and retain polar molecules.

A substance can easily enter a membrane when the partition coefficient (membrane/vehicle) is high it cannot easily leave the membrane when the partition coefficient (receptor solution/membrane) is low In complex structures such as the skin where the membrane may be nonpolar and the receptor tissue fluids polar a substance whose partition coefficient between polar and nonpolar solvents is nearly 1 0 will have the highest penetration rate Thus, permeability is more rapid if there is some but not too much affinity between a penetrating molecule and a membrane. Under these conditions the membrane will attract the penetrating molecule but not so strongly that it fails to release it on the other side.

Ions penetrate biological membranes slowly by diffusion Expenditure of cellular energy is often required for ion transport it is always required when transport occurs against a concentration gradient The enzymes and other types of metabolic machinery which assist ions across membranes may be absent from the skin

Q is the ratio of velocities of diffusion determined at absolute temperatures 10 K apart The more slowly a molecule penetrates a membrane the higher the Q_{10}. Measurement of Q can be a valuable tool in permeability studies

By studying the permeability of a membrane to a series of polar and nonpolar substances at different temperatures it is possible to formulate some reasonable idea of the chemical and physical nature of the pathways in the membrane If a series of nonpolar substances penetrates a membrane more rapidly than does a series of polar substances, the membrane is composed of lipid at the sites of penetration In a lipid membrane of this kind the Q_{10} increases markedly as —OH groups are introduced into the penetrating substance Additional —CH groups elevate the Q_1 only slightly

The rate of permeability per unit area times the square root of the molecular weight ($P \times M$) is constant for diffusion of substances through liquids or very permeable membranes with large pores When the membrane is less permeable $P \times M$

declines rapidly as the molecular weight of the penetrating substances increases. It reaches zero when the size of the molecular pathways through the membrane equals the size of the molecules of the penetrating substance.

In a complex membrane like the skin the overall permeability characteristics are probably a function of the most resistant, or limiting portion of the membrane i e., the barrier There fore, data of the type just discussed when obtained from the whole skin or from epidermis would provide information about the nature of the barrier

Most biological membranes are thought to consist of oriented double layers of lipid molecules to whose polar groups protein chains are attracted. The fact that these protein chains are crosslinked by hydrogen bonds, and by ionic, ether disulfide and other linkages renders the membrane mechanically stable (25) Whether or not there is a structure similar to this in the barrier of the epidermis is not yet known but certain experimental work suggests that this may be the case.

Experimental Studies on Skin Permeability

The previously mentioned studies by Rein (6) showed that ions do not pass through the epidermal barrier Rein believed that the transfer of ions is blocked by the negative electric charge of the barrier Recent experiments with radioisotopes show however that very small amounts of ionic material can pass through the barrier (16 17)

Rothman (9) in 1943 pointed out that lipid-soluble substances penetrate the skin more readily than polar substances and that substances soluble in both lipids and water penetrate most rapidly of all In support of Rothman s concept Treherne (20) in 1956 obtained quantitative data on the permeability of excised human skin to a series of radiotagged substances. He showed conclusively that the permeability of skin is directly proportional to the ether/water partition coefficients of the

following penetrating substances ethyl iodide methanol ethanol thiourea glycerol urea and glucose. The product, $P \times M^{*}$ was not constant for whole skin but was constant for dermis. These data support the concept that a lipid structure is present at the sites of epidermal penetration In the dermis it is clear that penetration occurs through a liquid medium

The penetration of water through skin is a special problem because of the high concentration of water within the body It is clear that water is lost by diffusion through skin tissues as well as by sweating (16) Table II is a compilation of the

TABLE II Los f w ter from the epidermal surf e f huma skin (mg/cm h)

Reference	Li ng ma (30° C)	Ex sed (35–37 ( )
Ikeuchi and Kuno (26)	1 0 (forearm)	–
Burch and W nsor (27)	0.2 (epigastri)	0.2 (epigastric)
Felsher and Rothma (28)	1 5 (f rearm)	–
Blank (8)	–	0 6 (bdomen)
Mal (3)	3 0 (back)	0 6 (ba k)

quantitativ data on diffusion of water from normal human skin (in the absence of sweating) which have been published by a number of investigators (3,8 26–28) The variations in these data may result from variations in the type of methods used and the fact that studies were made on different parts of the body More work is needed to support Mali s contention that 80 per cent of the *in vivo* loss of water in the absence of sweating takes place through the sweat ducts (3)

Water can pass int the body through the skin by exchange but there is no net transfer inward The inward passage of

water has been demonstrated by experiments with deuterium oxide (D_2O) (29) and tritium oxide (HTO) (30 31) Water penetrated into the skin of living man at the rate of 1.5 mg/cm²-hr Pinson (30) reported that the HTO diffusion rate out of the skin equals the HTO diffusion rate into the skin.

Pinson (30) showed that heating the skin increases its permeability to water But few quantitative data have been obtained with which to calculate Q for diffusion of water through skin Blank is in process of gathering such data. His preliminary experiments indicate a Q_{10} value of approximately 2

There is no evidence that substances move into the skin against a concentration gradient. As excised skin dies, its permeability to any given substance neither increases nor declines. This indicates that the barrier remains intact and that penetration of most chemical agents through the skin requires no energy from cellular metabolism Penetration is therefore entirely a process of diffusion

Very little satisfactory quantitative information has been reported concerning the permeability of skin to substances other than water The papers reviewed by Laug (15) Rothman (16) and Malkinson (17) do not contain sufficient data to permit calculation of rates of permeability Q_s, and other mathematical expressions which might assist our understanding of the nature of the barrier and its permeation mechanisms. There is entirely too much variation in the penetration values of the small group of substances already studied to permit one to draw general conclusions for all classes of substances. Many more studies must be made, as Cullet emphasized in his interesting discussion of permeability of the skin (19)

While we have evidence that the tough keratin mesh of the epidermis, with some sort of lipid protein structure at the sites of permeation probably constitutes the apparatus by which the skin protects underlying body tissues we need more detailed information about these structures. Further investigations should include measurement of the permeability of skin to many series of related substances. These groups of sub-

stances should be so selected that only one property at a time varies within each group e.g molecular weight and shape, polarity and charge partition coefficient. If data so obtained are to characterize intact skin it is important that the epidermal barrier should not be injured by the substances tested. Mustard gas, for example would not provide data about normal permeability because the first few molecules which penetrate probably destroy the barrier and allow abnormally rapid penetration by the molecules which follow

After data for intact whole skin have been secured comparable studies should be made with the isolated barrier Mali (5) has already studied the permeability of the isolated barrier to water In interpreting permeability data obtained with the barrier as isolated by the methods of Mali (5) and Szakall (11) the investigator must be alert to the possibility that the barrier may no longer be functionally intact. Measurement of the electrical conductivity of the isolated barrier might be a reliable means of determining whether it is uninjured.

Measurement of permeability before and after extraction of epidermis with polar and nonpolar solvents may reveal valuable information about the chemical structure of the barrier The great problem in such a study would be to locate with precision the sites from which material had been extracted Electron microscopy may be useful for this purpose More than the barrier may be extracted if the solvent is too destructive

Practical Considerations

The effect of physical and chemical trauma on the protective function of the skin may be of great practical importance for such trauma may permit the easy entry of toxic substances which would not penetrate intact skin in significant amounts. The sensitizing catechols of the poison ivy plant for example when applied to scratched or inflamed skin cause a much more severe reaction than when applied to intact skin

The same holds true for substances of therapeutic value

Hydrocortisone, applied topically to inflamed skin in which the barrier is broken rapidly penetrates to relieve the inflammation By blocking inflammation hydrocortisone allows the barrier to heal more rapidly but in so doing it cuts off further significant penetration of hydrocortisone. It is probably for this reason that some inflammatory diseases of the skin are benefited only briefly by topical hydrocortisone

The effectiveness of the skin as a protective organ ultimately depends on its ability to create and repair the barrier If the body has difficulty in restoring the barrier or if an individual expects to be exposed to agents likely to damage the barrier external protective devices may be used to replace or supplement the skin s activity Barrier creams have not proved to be as effective as early enthusiastic reports indicated Clothing made of impervious materials, such as rubber or synthetic substances, is the only safe external protective measure available today

REFERENCES

1 Witten, V H Studies of thorium X applied to human skin I Routes and degree of penetration and sites of deposition of thorium X in selected vehicles. *J Invest Dermatol 17* 311 322 (1951)

2. Rothman S. The principles of percutaneous absorption *J Lab Clin. Med 28* 1305-1321 (1943)

3 Mali, J W H The transport of water through the human epidermis. *J Invest Dermatol 27* 451-469 (1956).

4 Blank I H Griesemer R. D and Gould, E The penetration of an anticholinesterase agent (sarin) into skin. II Autoradiographic studies. *J Invest. De mat l 30* 187 191 (1958).

5 Scott, A., and Kalz, F The penetration and distribution of C -hydrocortisone in human skin after its topical application *J Invest Dermat l 6* 119-158 (1956).

6 Rein H Experimentelle Studien ueber Elektroendosmose an ueberlebender menschlicher Haut. *Z. Biol., 81* 1_5-140 (1924)

7 Rothman, S. Die Resorption durch die Haut In H Bethe, *Handb d norm u path Physiol 4* 107 151 (1929)

8 Blank, I. H Further observations on factors which influence the water content of the stratum corneum *J Invest Dermatol 12* 259-269 (1953)

9 Wolf J Der Oberflächenrelief der menschlichen Haut. *Z. mikroskop-anat Forsch. 47* 351-400 (1910)

10 Pinkus, H Examination of the epidermis by the strip method of removing horny layers. *J Invest Dermatol 16* 383-386 (1951)

11 Szakall, A. Hautphysiologische Forschung und Gesunderhaltung der Haut. *Fette Seifen Anstrichmittel 53* 399-405 (1951)

12 Blank I H Griesemer R D and Gould, E. The penetration of an anticholinesterase agent (sarin) into skin I Rate of penetration into excised human skin. *J Invest Dermatol 9* 299-309 (1957)

13 Levine, M Measurement of electrical skin resistance. *Arch. Neu ol Psychiat 29* 828-819 (1933)

14 Griesemer R D Unpublished experiments.

15 Calvery H O Draize J H and Laug, E. P The metabolism and permeability of normal skin *Physiol Revs 6* 495-510 (1946)

16. Rothman S *Physiology and Biochemistry of the Skin* University of Chicago Press, Chicago 1954 Pp 26-59.

17 Malkinson F D Radioisotope techniques in the study of percutaneous absorption *J Soc Cosm tic Chemists* 109 1?1 (1956).

18 Higuchi T *Permeation of Mechanical Barriers by Chemical Agents* Med Lab Contract Report No 32, Army Chemical Center May 19 1

19 Guillet, M Physicochemical conditions of cutaneous absorption. Part I *J physiol (Paris) 46* 31-49 (1951)

20 Treherne J E The permeability of skin to some non-electrolytes. *J Physiol (London) 133* 1 1 180 (1956)

21 Selby C. C. An electronmicroscopic study of thin sections of human skin. II Superficial cell layers of footpad epidermis *J Invest Dermatol 29* 131 150 (1957)

22. Stoughton R Relation of the anatomy of normal and abnormal skin to its protective function This volume p 3

23 Matoltsy A G and Balsamo C. A A study of the components of the cornified epithelium of human skin. *J Biophys Biochem Cytol 1* 339-360 (1955)

24 Matoltsy A G and Herbst, F S. M. A study of human epidermal proteins. *J Invest Dermatol* 26 339-342 (1956)
25 Davson H and Danielli J F *The Permeability of Natural Membranes*. Cambridge University Press, Cambridge England, 1952.
26 Ikeuchi K and Kuno Y On the regional differences of the perspiration on the surface of the human body *J Oriental Med* 7 67-89 106-107 (1927)
27 Burch, G E., and Winsor T Rate of insensible perspiration (diffusion of water) locally through living and through dead human skin. *Arch Intern Med* 74 437-444 (1944)
28. Felsher Z and Rothman S. The insensible perspiration of the skin in hyperkeratotic conditions. *J Invest Dermatol.* 6 271 278 (1945).
29 Szczesniak, A. S., Sherman H and Harris, R. S. The percutaneous absorption of water *Science 113* 293-294 (1951)
30 Pinson, E A Water exchanges and barriers as studied by the use of hydrogen isotopes. *Physiol Revs.*, 32 123-134 (1952).
31 De Long, C. W Thompson, R C., and Kornberg, H A Percutaneous absorption of tritium and tritium oxide. Hanford Atomic Products Operation 5., 1953

Discussion

Dr. Kondritzer (Army Chemical Center Maryland) Is it your contention that penetration through the epidermis takes place by true diffusion (i.e thermal diffusion or by flow through orifices and capillaries? If it is penetration by thermal diffusion, proof of this mechanism would come from the determination of the temperature depending on the process and the construction of an Arrhenius plot. In practice this may be extremely difficult to accomplish and may prove to be a stumbling block If penetration is by flow through pores and capillaries (the work of Selby may indicate this to be the case) the effect of temperature on the rate would be low or not great.

Dr. Griesemer Very few studies have been reported on the effect of temperature on permeation of chemical substances through the skin. It is our hope that your questions, Dr Kondritzer will stimulate more work on the effect of temperature. Dr Irvin H Blank, in our laboratories, is now investigating the effect of temperature on water permeation of skin. Only after nonpolar and other polar sub-

stances have been investigated will sufficient temperature data be available to help decide whether diffusion or capillary flow is the important physical factor in skin permeability

DR. SULZBERGER I would like to point out that in histochemical studies and in radioautographic sections, fixation should be gaseous to prevent liquids from carrying the applied material from the surface and into the tissue by diffusion from the edges and below Also all cutting must be from within outward, with a clean blade each time to prevent carrying material from the surface into the tissue with the knife-edge Using these techniques, MacKee Herrmann and I showed that the principal route of penetration of topically applied sulfonamides was via the follicular openings and through the follicular wall at about the level of sebaceous gland openings. Moreover Witten's radioautographic work with thorium X penetration obviates the doubts as to whether the change in the photographic silver emulsion is due to the actual presence of the radioactive molecule at the site of change or to the action of the energy emanating from molecules still at the surface With thorium X one can localize the four-pronged star of the alpha particle in the tissues.

DR GRIESEMER Dr Sulzberger's remark about the precautions needed in fixation and cutting to avoid diffusion and contamination point out very clearly some of the technical problems encountered in autoradiography In our work with sarin since the tissue remained frozen during cutting and exposure of the photosensitive emulsion, diffusion was minimal. Moreover our autoradiograms showed little or no sarin in the dermis, and this sarin was distributed so diffusely that it is doubtful whether contamination from the knife blade could have accounted for it Sarin did not penetrate deeply into the follicles Therefore it is more likely that sarin reached the dermis by passing directly through the epidermis Of course one cannot exclude the possibility that sarin may have penetrated follicles, sebaceous glands, and sweat glands as well as the epidermis. The autoradiographic work with thorium X, which Dr Sulzberger mentioned (reference 1) was, I believe interpreted by Witten to indicate that thorium X had no preferential pathway of penetration

I think that when one focuses attention so intensely on such subtle points as avenue of penetration and uses dramatic devices like *autoradiography, it is very easy to lose perspective It is tempting to* think that those little black granules in the autoradiograms indicate significant permeation of the skin Actually only a few molecules are needed to produce the effect Direct chemical analysis or quantitative measurement of radioactivity must be utilized for accurate de

termination of rates of penetration. Radioactivity data should be converted to moles if one wishes to appreciate its significance. For example, when this is done for radioactivity measurements in urine after application of radioactive substances to the skin surface an almost infinitesimal amount of substance appears to have penetrated the skin.

DR. MARZULLI (Army Chemical Center Maryland) Although you were unable to find penetration into the hair follicles by sarin, with an autoradiographic technique, scientists at Porton England, with a similar technique, have reported that it does penetrate the hair follicles. At our laboratories, we have used a fluorescent tracer substance (the tracer material was tested by application to the skin surface as a 1 99 solution in the sarin-like material, and recovery in the subdermis in the same proportion 1 99 after penetration of the skin) to trace the pathway of sarin-like material through the skin of monkeys (*in vivo*) We concluded that the tracer substance and probably the sarin-like material penetrated the pilosebaceous apparatus and eccrine sweat glands as well as transepidermally By means of this technique, the barrier was found, as Rothman and Rein have postulated to be much thinner than the entire thickness of the stratum lucidum. Its location appeared to correspond to the junction between stratum lucidum and stratum germinativum. Penetration of the stratum lucidum was accomplished within 90 seconds whereas the barrier was not penetrated for 30 minutes or more.

DR. BLANK. While, in general autoradiographic techniques have supplied much valuable information, it must be remembered that they are subject to much misinterpretation. With radiophosphorus, one may get darkening of the photographic plate at some distance from the actual site of the phosphorus atom.

I too, have seen some of the autoradiograms made at Porton, England they may or may not be the same ones to which Dr Marzulli has referred. These autoradiograms did show more darkening within the hair follicles than did ours. But darkening within the hair follicle or even a short distance around the hair follicle does not indicate that sarin has necessarily penetrated farther than the follicle or that the route of penetration into the deeper layers of the skin has necessarily been through the hair follicles. As Dr Griesemer has said, only a series of autoradiograms from sections of skin taken at increasing time intervals following the application of the sarin and showing a progression of the sarin along some pathway as the time lengthens, will actually reveal the route of penetration.

DR. GRIESEMER. Data obtained with a fluorescent label combined

with sarin must also be carefully interpreted One has to be sure that the label and the sarin follow the same route.

I agree that the major barrier in the skin is near the stratum lucidum and that the sarin rapidly penetrates the entire stratum corneum and possibly the stratum lucidum but it penetrates through the major barrier much more slowly

PROTECTION AGAINST THE INVASION OF BACTERIA AND FUNGI

IRVIN H BLANK

Department of Dermatology Harvard Medical School
Massachusetts General Hospital Boston Massachusetts

The protection which the integument provides against transfer of matter was discussed earlier This paper will deal with the protection offered by the integument against the invasion of bacteria and fungi Both forms of protection are important in the maintenance of general health Actually the skin plays an important role in the protection of other organs from invasion by bacteria but in so doing the skin itself may become invaded if it continues to protect the other organs it must hold the invading microorganisms within itself I shall here discuss first the ways in which the skin is able to maintain a limited surface flora of bacteria and fungi I shall then consider the underlying structural barrier against invasion from the environment and the subepidermal defenses against invasive organisms. Finally I shall discuss various manifestations of inadequate defense.

Surface Defenses

RESIDENT FLORA

A well-established flora of bacteria resides on the cutaneous surface This resident flora consists principally of *Micrococci Diphtheroids* (*Corynebacteria*) and *Propionibacteria* (1) The skin furnishes adequate nourishment for these organisms they reproduce and maintain a relatively constant population Surely

TRANSIENT FLORA

Organisms not indigenous to the cutaneous surface are rarely able to establish residency on the skin. Among the factors which prevent them from actively multiplying and becoming a part of the resident flora are (*a*) the low moisture content of the stratum corneum and (*b*) the presence on the skin surface of naturally produced antibacterial substances. A microorganism like *Micrococcus pyogenes* var *aureus* which is not usually a member of the resident flora, but for which the stratum corneum supplies nutrition adequate to support active multiplication does not grow and multiply unless adequate moisture is present (5). If it cannot multiply it soon dies. Thus lack of moisture in the stratum corneum prevents potentially invasive organisms from gaining a foothold on the surface of the skin.

For another reason the cutaneous surface is not conducive to bacterial multiplication. Measurements of acidity on the normal cutaneous surface show the range of pH to be 4.5 to 6.0. From such observations, the acid mantle concept developed, and this has been thought to be an important factor in the autogenous sterilization of the cutaneous surface (6). It has been shown, however, that many bacteria which fail to grow on the cutaneous surface can grow *in vitro* in much more acid environments. This indicates that the low pH alone does not prevent the bacteria from multiplying. The acid reaction results from the secretion by the sebaceous and sweat glands of organic acids or substances which yield organic acids on hydrolysis. Some of these organic acids, such as caprylic and lactic acid have specific antibacterial properties (7); others such as capric and undecylenic acid have antifungal properties (8).

Thus the first line of defense against bacterial invasion is the establishment of an environment which is unfavorable for the growth and multiplication of most bacteria except those few relatively harmless species which constitute the resident flora. The lack of moisture and the presence of specific antibacterial and antifungal organic acids are the two most important factors in making the cutaneous surface unsatisfactory for the growth

PROTECTION AGAINST THE INVASION OF BACTERIA AND FUNGI

IRVIN H BLANK

Department of Dermatology Harvard Medical School
Massachusetts General Hospital Boston Massachusetts

The protection which the integument provides against transfer of matter was discussed earlier This paper will deal with the protection offered by the integument against the invasion of bacteria and fungi Both forms of protection are important in the maintenance of general health Actually the skin plays an important role in the protection of other organs from invasion by bacteria, but in so doing the skin itself may become invaded if it continues to protect the other organs it must hold the invading microorganisms within itself. I shall here discuss first the ways in which the skin is able to maintain a limited surface flora of bacteria and fungi I shall then consider the underlying structural barrier against invasion from the environment and the subepidermal defenses against invasive organisms. Finally I shall discuss various manifestations of inadequate defense.

Surface Defenses

RESIDENT FLORA

A well-established flora of bacteria resides on the cutaneous surface This resident flora consists principally of *Micrococci Diphtheroids* (*Corynebacteria*) and *Propionibacteria* (1) The skin furnishes adequate nourishment for these organisms they reproduce and maintain a relatively constant population Surely

they do not cause any disease in the true sense of the word as long as they remain on the surface Even when they penetrate below the surface these resident organisms are not considered to be pathogenic. It is not definitely known whether they can produce disease but if they can do so the conditions under which this is possible probably occur very rarely

It is desirable that the rate of reproduction of the surface bacteria be minimum for two reasons With the chance that some of these bacteria might become invasive under rare conditions it is advisable to have a small bacterial population A cosmetic reason for controlling the bacterial multiplication is that body odor has been shown to be caused mainly by bacterial decomposition of cutaneous secretions (2)

The rate of reproduction of bacteria on the surface of the skin depends in part on the moisture content of the cornified epithelium There is adequate moisture for reproduction of bacteria on the skin of normally sweating axillae groins, palms and soles In the axillae and groins the moisture comes from both apocrine and eccrine sweat glands—more from the eccrine than from the apocrine Apocrine sweat contains substances which though odorless at the time of secretion undergo bacterial decomposition and become odorous. Pure eccrine sweat is odorless and is thought to remain odorless even after bacterial growth Eccrine sweat picks up lipids and proteins from the cutaneous surface and these substances produce odors when they undergo bacterial decomposition Thus, moist areas of the skin which have no apocrine glands (soles) can also become odorous. Among the resident flora of the skin the diphtheroids and micrococci are thought to be responsible for most of the odor (3)

The moist areas of skin possess no adequate natural defense against the development of odor We must depend therefore on artificial means if we wish to prevent odor formation The use of antiperspirants somewhat reduces the amount of *moisture delivered to the cutaneous surface by the sweat glands,* but this reduction is not sufficient per se to prevent multiplication of bacteria. Most antiperspirants are also however

antibacterial agents, and they therefore retard bacterial multiplication even in the presence of adequate moisture

Good hygiene with regular soap can hold the resident bacterial population at a minimum and, by frequent removal of the odorous products can prevent the development of strong odor Some of the recently developed antiseptic compounds which have been added to soap such as hexachlorophene and tetramethylthiuram disulfide adhere to the cutaneous surface. When such soaps are regularly used enough of the antibacterial agent remains on the skin to retard multiplication of the surface bacteria, even when adequate moisture is present. Thus, the development of odor is diminished These antibacterial agents are not good germicides and they do not reduce the bacterial population by killing the bacteria rapidly They are principally bacteriostatic not bactericidal

In areas of the skin which are not supplied with actively secreting sweat glands and are not covered with occlusive clothing the stratum corneum is usually relatively dry Most of the moisture in this tissue must come from the moist structures which lie underneath the major barrier of the skin. Since the major barrier in the skin is in or near the base of the stratum corneum it separates the upper part of the stratum corneum from its source of moisture. The amount of water present in the stratum corneum at any given time must depend upon the relation between the rate at which it receives water through the barrier from the underlying tissues and the rate at which it loses water to the environment (4) The rate at which the stratum corneum receives water from the underlying tissues is a function of the permeability of the barrier and the rate at which it loses water is a function of the vapor pressure of the environment. Only at high relative humidities will the stratum corneum of nonsweating, normal skin retain enough water to support the multiplication of bacteria (5) Different species of bacteria require different amounts of water for growth and multiplication The number of bacteria per unit area, their rate of reproduction and the resulting odor level are all lower on the dry areas of skin than on the moist areas.

TRANSIENT FLORA

Organisms not indigenous to the cutaneous surface are rarely able to establish residency on the skin Among the factors which prevent them from actively multiplying and becoming a part of the resident flora are (a) the low moisture content of the stratum corneum and (b) the presence on the skin surface of naturally produced antibacterial substances. A microorganism like *Micrococcus pyogenes* var *aureus* which is not usually a member of the resident flora but for which the stratum corneum supplies nutrition adequate to support active multiplication does not grow and multiply unless adequate moisture is present (5) If it cannot multiply it soon dies Thus lack of moisture in the stratum corneum prevents potentially invasive organisms from gaining a foothold on the surface of the skin.

For another reason the cutaneous surface is not conducive to bacterial multiplication Measurements of acidity on the normal cutaneous surface show the range of pH to be 4.5 to 6.0 From such observations, the acid mantle concept developed and this has been thought to be an important factor in the autogenous sterilization of the cutaneous surface (6) It has been shown however that many bacteria which fail to grow on the cutaneous surface can grow *in vitro* in much more acid environments This indicates that the low pH alone does not prevent the bacteria from multiplying The acid reaction results from the secretion by the sebaceous and sweat glands of organic acids or substances which yield organic acids on hydrolysis Some of these organic acids such as caprylic and lactic acid have specific antibacterial properties (7) others, such as capric and undecylenic acid have antifungal properties (8)

Thus the first line of defense against bacterial invasion is the establishment of an environment which is unfavorable for the growth and multiplication of most bacteria except those few relatively harmless species which constitute the resident flora The lack of moisture and the presence of specific antibacterial and antifungal organic acids are the two most important factors in making the cutaneous surface unsatisfactory for the growth

of microorganisms By holding the surface bacterial population at a minimum one reduces the likelihood that pathogenic organisms will be present to invade the tissues, if the other protective functions of the skin prove inadequate.

Structural Barrier

Histologic sections of normal skin seldom reveal any microorganisms except those on the surface of the skin Under abnormal conditions O Brien has demonstrated bacteria in the sweat ducts and hair follicles (9) The smallest dimension of the smallest bacterium is approximately 200 mμ. A virus may be one-tenth this size Since the outer part of the stratum corneum is loosely held together and is being shed continuously it is conceivable that there might be holes here large enough for bacteria to enter this portion of the stratum corneum. The more compact lower part of the stratum corneum (barrier) is unlikely to contain many holes as large as even the small bacteria This barrier probably extends at least part way into the hair follicles. Therefore a bacterium which enters the hair follicle would still have to traverse the barrier before it could actually enter the skin. A pathway into the tissues via the sweat duct might be more easily followed since no compact barrier is known to line the sweat duct. There is, however little evidence that bacteria actually do enter by this pathway

Bacteria carry an electronegative charge. One might hope that the cornified epithelium were electropositively charged so that those bacteria which found openings through the skin large enough to permit their passage would be held on the walls of the openings by electrostatic attraction Unfortunately this does not appear to be the case in the cornified epithelium Although the pH of the cutaneous surface is less than 7 0 the proteins in this tissue are probably still on the alkaline side of their isoelectric point and probably carry a negative charge (10) They therefore would repel negatively charged bacteria

The structural barrier is, then the second line of defense of the skin If this barrier always remained intact it might

serve adequately to protect man against all bacterial invasion Unfortunately however even though the epidermis appears to have a relatively high tensile strength it seems likely that very small mechanical breaks in the barrier must occur not infrequently considering the many stresses to which the skin is subjected Small though these breaks are they are large compared to the size of the bacteria Small numbers of bacteria must penetrate the structural barrier via these breaks Fortunately the skin under the barrier can muster still other defenses, and only under special conditions do the bacteria spread to other organs or grow and reproduce to the point of producing pathology in the skin.

Subepidermal Defenses

Only after they have penetrated the structural barrier can the microorganisms be considered to be actually within the body of the host. Once they are within the body the defenses which the skin can muster against them are probably no different from those which can be used by any other organ Anatomically the skin may be somewhat better suited than some other organs for dealing with the invasion of microorganisms. For instance the skin is relatively rich in lymphatics. In general however defense mechanisms in the skin are the same as in other organs of the body (*a*) containment, (*b*) phagocytosis, (*c*) action of antibacterial substances and (*d*) formation and action of antibodies.

This phase of the protective mechanisms of the skin could be adequately discussed only by a group representing various disciplines and including a bacteriologist a hematologist an immunologist, a physical chemist and a physiologist Since the protective mechanisms involved are not unique to the skin it is necessary here only to mention briefly certain facets of the subject and t refer t some comprehensive reviews such as those of Miles (11) Dubos (12) Elberg (13) and the recent symposium on natural resistance to infection (14)

All the subepidermal defense mechanisms can be grouped

under the general term "host resistance. While adequate host resistance may imply that major pathology within the host will not develop it does not necessarily imply that pathology within the skin itself will not develop. Actually cutaneous lesions may occur as a result of the activity of the skin in containing the bacteria within itself thus preventing their spread to other organs. Inflammation almost always accompanies the defense and indeed may constitute a part of it (15)

CONTAINMENT

Below the epidermal barrier of normal skin bacteria en counter in the skin no major structure which can prevent their systemic dissemination with the possible exception of the blood vessel walls. A more general consideration of the influence of the local blood supply on the primary lodgment of bacteria in a given area of skin has been presented by Miles (11) The local blood supply is particularly important during the early hours of invasion In experiments in which adrenaline was used to produce vasoconstriction at the moment of injection of bacteria the resulting local lesions were much larger and the death rate was much higher than when vasoconstriction had not been evoked. Cutaneous circulation and vascular reactions are discussed in detail in another paper in this volume.

Of course bacteria need not penetrate directly from the skin into capillaries in order to reach the blood stream Apparently the walls of the lymphatics offer very little resistance to the transfer of bacteria. Most of the organisms which are not held within the dermis probably enter the lymphatics rather than the capillaries. From the lymphatic system they may then enter the blood stream. Fortunately in most areas of the body the bacteria must pass the lymph nodes before they can enter the blood stream and the lymph nodes constitute a major struc tural barrier against their transmission.

In inflamed skin, a fibrin clot forms which also becomes a structural barrier Hughes (16) has studied fibrin films formed *in vitro* and has shown that they are capable of retaining micro-organisms but permit the passage of leukocytes.

The true isoelectric point of the proteins in connective tissue remains unsettled. If in normal or inflamed dermis it could be shown that these protein structures were on the acid side of their isoelectric point their net surface charge would be positive The bacteria would carry an electronegative charge and would therefore be attracted to and held by the surface of the connective tissue fibers.

Any clumping or agglutination of the bacteria which occurs at the site of invasion will facilitate containment of the bacteria. Agglutination may occur if the host has been invaded previously by the same organism and has developed agglutinating antibodies specific to the bacteria

The edema which accompanies inflammation works against containment. Larger interfibrillar spaces filled with fluid form better channels for the easy transport of bacteria.

One school of thought is now questioning the protective value of containment of invading bacteria within the skin and lymph nodes (11) Experimental work has shown that mice can tolerate larger numbers of some pathogens after intravenous injection than after subcutaneous injection Possibly there are tissues and cells in other organs of the body which can deal with some bacteria more effectively than can the skin and lymph nodes. If this is correct then containment within the skin i not necessarily the most efficient way f protecting the body against systemic infection

PHAGOCYTOSIS

It is not definitely known why numerous phagocytic cells reach a given area of the dermis soon after the arrival of bacteria. The phagocytic cells are thought to be attracted from other tissues by some chemotactic mechanism For a number of years, the surface charge on the bacterium and the phagocyte has been thought to influence the movement and the activity of the phagocytes. In 1928 Falk (17) considered this phase of the problem to be unsolved More recently in a complete review of the subject of phagocytosis, Berry and Spies (18) discussed

the interrelationship between surface charge and the free surface energy on the phagocyte and bacterium

The free surface energy on a phagocyte determines its interfacial tension which in turn influences its movement in liquids and along surfaces. Phagocytes seem not to move easily through a liquid medium but they do move along a solid surface. The fibrin threads in an inflamed area may provide such a surface.

The complex mechanisms which control the movement of phagocytes toward bacteria and their ability to enclose, contain and sometimes kill the bacteria are not yet completely understood.

Tompkins and Crillo (19) found that when killed tubercle bacilli were injected subcutaneously into mice the reticulo-endothelial cells of the subcutaneous tissue (the so-called wandering cells) were the active phagocytic cells during the first 12 hours following injection After this interval the polymorphonuclear leukocytes reached the site of injection and subsequently both types of cells phagocytized the bacteria A more complete discussion of the types of fixed and wandering cells capable of phagocytizing bacteria may be found in the textbook by Wilson and Miles (20)

Thus far in our discussion of defensive factors we have considered mostly those factors which apply to any microorganism and which are present in the host whether or not there has been previous invasion by an organism We have considered only one adaptive or acquired factor It is recognized that phagocytosis takes place the first time that a given organism invades the host. The phagocytic process is more efficient however if the host has previously been invaded by that organism and has successfully overcome the invasion Antibodies developed by the host during the first invasion can so alter the organisms of a subsequent invasion that they can be more efficiently engulfed by the phagocytes

Many microorganisms are not killed as a result of phagocytosis some appear to be able to live and multiply intracellularly They may actually be protected against antibodies when

they are held within the phagocyte It has been suggested that if on the other hand the defenses of the skin and the blood and lymphatic systems are inadequate to kill invading microorganisms the phagocytes may contain them while they are being transported to an organ in which they can be destroyed

ACTION OF ANTIBACTERIAL SUBSTANCES

Just as some of the products of secretion on the cutaneous surface have certain antibacterial properties, some substances in the internal tissues are capable of killing certain organisms An example of this which has received much attention recently is the properdin system of the blood (14) The activities of substances, such as the basic peptides, the heme compounds spermine lipids, organic acids, and enzymes (lysozyme) are discussed by Dubos (19) and are reviewed by Elberg (13) All these substances are nonspecific agents used by the host in its defense against invasive microorganisms.

The properdin system is limited to the blood stream Many of the other substances are found both intra and extracellularly in other tissues. The dermis is not known to be particularly rich in any of these chemicals.

FORMATION AND ACTION OF ANTIBODIES

Most of the protective mechanisms which have been discussed so far are independent of any adaptive processes within the host. Immunity which consists of the development and activity within the host of antibodies against invading microorganisms is essentially adaptive in character The entire subject of immunity has been comprehensively reviewed in recent years in *Topley and Wilson's Principles of Bacteriology and Immunology* (20) and in Raffel's *Immunity Hypersensitivity and Serology* (21) No attempt will be made here therefore to discuss the formation and activity of antibodies against invading microorganisms, except as these processes are manifest in the skin

Few if any antibodies are thought to be formed by cells that

are considered to be part of the skin itself They are formed however by certain cells of the lymphoid macrophage system which includes the reticulo-endothelial system and the macrophages (90) Small amounts of antibody could be formed by cells of the lymphoid macrophage system which are present in the skin In an immune host amounts of antibody larger than would be formed in the skin are brought to the skin by the blood stream and tissue fluids at the time of a bacterial invasion After inflammation occurs at the site of invasion the fibrin clot may hinder the transfer of antibody from surrounding tissue (16) The possibility of localized specific immunity in skin is unsettled

The host produces multiple antibodies to any foreign material which is as chemically complex as a bacterium Many of these antibodies act by enhancing other defense mechanisms and probably seldom act alone It has been pointed out that an antibody which causes agglutination of bacteria may aid in their containment at the site of invasion and that the combination of antibodies with invading organisms makes them more susceptible to phagocytosis. For a few invading organisms it can be shown that, together with complement, the antibody appears in some way to alter the organism so that it subsequently undergoes lysis and is thus destroyed.

There is an extensive literature on the inflammatory reaction which often accompanies the combination of antigen with antibody When inflammation occurs, it is this part of the antigen-antibody reaction which is customarily associated with hypersensitivity of the host. When the antigen is part of an invading organism and when the inflammation occurs at the site of invasion we do not know definitely whether the inflammation is helpful to the host in its effort to overcome the invading organisms. Raffel (91) separates acquired resistance from hypersensitivity He states that at the present time "there exists no basis for regarding the hypersensitive reaction as part of the mechanism of resistance to infectious disease" This point of view is not shared by all immunologists. It should be

kept in mind, however that if all terms were carefully defined there might be less difference of opinion than there now appears to be

Immune mechanisms undoubtedly play a major role in the host's defense against invasion of microorganisms, but the skin itself probably does not play an important role in the process by which antibodies help the host to resist the invader

Inadequate Defense

In spite of the various protective mechanisms which have been discussed microorganisms at times successfully invade the skin and produce disease there. Also although it would be difficult to prove it seems possible that microorganisms might pass through the skin without producing disease localize in some other organ and cause disease at that point Whether an invasion is successful because of some specific characteristic of the invading organism or because of some temporary disturbance in the defense mechanisms of the host is seldom clear

Few if any bacteria can successfully penetrate the normal cornified epithelium No mechanism for locomotion which they may possess, such as flagellae can function under the conditions found on the cutaneous surface If a species of bacteria found favorable conditions for growth on the cutaneous surface and if it possessed a proteolytic enzyme system capable of liquefying keratin in the same way that some organisms liquefy gelatin then that species might be able to penetrate the stratum corneum If such bacteria exist they must be rare

The filamentous fungi which produce cutaneous lesions grow into the stratum corneum and into hairs and nails. Some species were shown to produce keratolytic enzymes. The more moist the stratum corneum the more easily the fungi appear to invade this tissue Dermatophytae fungi causing superficial ringworm diseases, invade only keratinized structures

The most vulnerable area of the skin appears to be the hair

follicle On an otherwise normal healthy skin it is not uncommon to find small scattered superficial pustules around hair follicles. It may be that the hair follicle simply provides a suitable site for the lodgment of large numbers of organisms which remain viable because the stratum corneum within the follicle is moist, or the structural barrier may become thin and weak within that portion of the epidermis which lines the hair follicle

When O Brien (9) placed large numbers of pathogenic organisms on the cutaneous surface he did not consistently produce lesions unless he covered the cutaneous area of inoculation with nutrient agar The moisture supplied by this nutrient agar probably aided the bacteria in invading the skin

Breaks frequently occur in the structural barrier of the skin That the subepidermal defenses are adequate to deal with the few bacteria which may enter through these breaks is shown by the infrequency with which lesions appear in the normal skin. Apparently the defenses are adequate unless large numbers of organisms penetrate to the subepidermal region. Elek (22) was unable to produce a furuncle in the skin of human volunteers by the intradermal injection of small numbers of staphylococcus pyogenes. Only when he injected 7.5×10^6 microorganisms could he consistently produce pus formation. When he placed a single suture in the skin which was contaminated with an estimated 100 microorganisms, however a pustular lesion resulted. It is not clear how the presence of the foreign body helped in overcoming the defenses of the host in this case the subepidermal defenses. One cannot say that the inflammation caused by a foreign body predisposes the skin to infection since previously mentioned publications indicate that inflammation often augments the defense mechanisms.

If microorganisms do penetrate the epidermal barrier and if any or all of the subepidermal defense mechanisms are inadequate then systemic bacterial disease may result. Under these conditions, the integument has failed to perform its primary function—that of protection Fortunately for man this seldom

happens. When it does happen we are rarely able to determine the specific fault in the host's resistance which accounts for the failure or the way in which any fault which becomes evident can be corrected. Although some progress has been made in understanding resistance to microorganisms much remains to be learned about the determinants of host resistance and the specific role of the skin in protecting man from the invasion of microorganisms.

REFERENCES

1 Pillsbury D M and Kligman A M Some current problems in cutaneous bacteriology In *Modern Trends in Dermatology* 2nd series, edited by R M B MacKenna, Paul B Hoeber New York 1951 Pages 187 215

2 Shelley W B, Hurley H J and Nichols, A C Axillary odor experimental study of the role of bacteria apocrine sweat and deodorants *Arch Dermat & and Syph ilol* *68* 430-446 (1953)

3 Strauss, J S and Kligman, A M The bacteria responsible for apocrine odor *J Invest Derm tol* 67 71 (1956)

4 Blank I H Factors which influence the water content of the stratum corneum. *J Invest Dermatol* *18* 433-440 (1952)

5 Blank I H and Dawes, R. K The water content of the stratum corneum. IV The importance of water in promoting bacterial multiplication on cornified epithelium *J Invest Derm tol* *31* 141 145 (1958)

6 Burtenshaw J M L. The autogenous disinfection of the skin. In *Modern Trends in De m tology* edited by R M B MacKenna. Paul B. Hoeber Inc New York 1948 Pages 158-185

7 Pillsbury D M and Rebell, G The bacterial flora of the skin. Factors influencing the growth of resident and transient organisms. *J Invest Derm tol* *18* 173-186 (195)

8 Rothman, S. Smiljanic A Shapiro, A L, and Weitkamp, A W The spontaneous cure of tinea cap ti n puberty *J Invest Dermatol* *8* 81 98 (1947).

9 O Brien, J P The etiology of poral closure II The role of staphylococcal infection in miliaria rubra and bullous impetigo. *J Invest Dermatol* *15* 102 133 (1950).

10 Blank, I H and Coolidge M H Degerming the cutaneous

surface. I Quaternary ammon um compounds. *J Invest. Dermatol* 15 219-256 (1950).
11 Miles, A. A. Reactions to Bacterial Invasion In *Lectures on the Scientific Basis of Medicine* III 1953-54 University of London The Athlone Press, London, 1955 Pages 235-258
12. Dubos, R. J *Biochemical Determinants of Microbial Diseases.* Harvard University Press, Cambridge, Mass., 1954
13 Elberg, S. S. Factors affecting resistance to infection *Ann Rev Microbiol. 10* 1 20 (1956)
14 Symposium on Natural Resistance to Infections. *Ann N Y Acad Sci 66* 233-414 (1956).
15 Rich, A R. Inflammation in resistance to infection. *Arch Pathol.*, 22 228-254 (1936)
16. Hughes, W H The fibrin barrier regarded as a filter in inflammation *Brit. J Exptl Pathol* 29 173-180 (1948).
17 Falk I S. In E. D Jordan and I S Falk, *The Newer Knowledge of Bacteriology and Immunology* University of Chicago Press Chicago, Ill 1928
18. Berry L. J and Spies, T D Phagocytosis. *Medicine 28* 239-300 (1949)
19 Tompkins, E. H and Grillo M A. Factors favoring phagocytosis by reticulo-endothelial cells early in inflammation *Am J Pathol 29* 217 231 (1953)
20 Wilson G S., and Miles, A. A. *Topley and Wilson Principles of Bacteriol gy and Immunology* Vol. II The Williams & Wilkins Co., Baltimore, Md. 1955
21 Raffel, S *Immunity Hypersensitivity and Serology* Appleton Century-Crofts, Inc., New York, 1953
22. Elek, S. D Experimental staphylococcal infections in the skin of man. *Ann N Y Acad Sci 65* 85-90 (1956)

Discussion

Dr. Sulzberger I want to comment on f ur different po nts in Dr Blank s excellent presentation. The first concerns antiperspirants. Although Dr Blank seems to think that the action of the aluminum salts in preventing the maintenance of moisture of the skin surface was negligible I think every woman who has had axillary perspiration nd has used the antiperspirants will testify that the staining of the garments and the moisture of the clothing and illae is much reduced nd there is no reason why this should not

play a substantial role in the maintenance of a certain degree of dryness or a less humid chamber for growth of microorganisms at the surface While I agree that there is no way in which one can keep the cornified epithelium from having a certain degree of hydration, I think surface moisture can be reduced by antiperspirants and that this may play some role in reducing the conditions propitious to the growth of bacteria

The second point I would like to make is that I believe, and I think most people will bear me out, that even one single thorough washing with one of the soaps containing so-called antibacterial agents will reduce the odor of the axillae for many hours, much longer than if one used a soap without such additives. This clinical observation is somewhat in contradiction to Dr Blank s statement that it requires chron c usage repeated use of these soaps to reduce the res dent flora s gnificantly I would like to know if he agrees with my statement, how he wo ld reconcile those two facts The redu tion of odor even after one an l the first washing and the lack of reduction of the resident flora as determined by bacteriologic assays.

The third point is one that I th nk is perhaps i uch more impor tant than these cosmetic ones nd is based on the work of Keller Herrmann nd Pisha who showed by staining with electronegati e nd electropositi e lyes that at the barrier layer of the epidermis there is a doubly charged membrane The neg tive charge is on the outside and the positive charge is inside. On the outs de one would get a repulsion of the microorganisms but those bacteria that hap- pen to get thro gh cou ld be attracted nd slowed by electrostatic forces on the positi e side. I would l ke to hear Dr Blank comments this.

The l st po nt I would like to make is that there re many more complicated conditions than he was able to mention which have to lo with host resi tance. One of the f rst pieces of work that I ever engaged in, in Bloch s Clini in Zurich, concerned tl e derma totropism of pathogenic fungi that p roduce dermatoph ytosis, fungi infection of the skin hair and nails When one infect gi inea p g kin with these fungi they p roduce disease on the skin urfa e One an find tl em only in tl e horny structures in the hairs and the horny layer of the k n su fa e in the guinea p ig However if one rubs them in well at the t me when the inflammation starts, bout 6 to 8 lays fter inoc lation one can recover these fungi from the blood stream. Still they cause no dise se of the blood And if one takes out the org ns of these guinea p gs nd p uts tl em into test t bes, and

denly these fungi begin to grow through these organs. One can see them as cultures in the liver in the kidneys, in the brain almost everywhere. So there is something about the skin, and the tissues of the internal organs that prevents these fungi from multiplying *in vivo* whereas they are able to multiply in the keratin at the skin surface. They are also able to multiply within the dead part of the lens as was shown by Werner Jadassohn. But they are not able to multiply on the cornea or within any other parts of the eye. So there is something that we call the necroph lia of these fungi. All living tissues seem to have the capacity of halting their propagation whereas in cornified materials and the material n any organ that is dead and removed from the body these fungi can multiply indefinitely

DR. BLANK. In respect to the antiperspirants, I certainly agree that they do tend to reduce somewhat the amount of sweat delivered to the cutaneous surface. By the experimental techniques we have used, we have been unable to show a very large reduction in the amount of sweat del vered to the cutaneous surface after the use of aqueous solutions of aluminum salts. We have also measured by experimental methods the amount of water that the corni fied epithelium must contain in order to support bacterial growth It is exceedingly difficult for me to believe that the small reduction of moisture delivered to the cutaneous surface which follows the use of antiperspirants could decrease the water content of the cornified epithelium sufficiently to prevent the multiplication of bacteria.

With respect to single washings with hexachlorophene soaps, I have tried to make it clear that immediately after a single washing with one of these soaps the resident flora on the cutaneous surface is no less than it would have been had one washed with a soap not containing this material. I have said that the hexachlorophene will be retained on the cutaneous surface and certainly a small amount of it will be retained after only a single washing. I see no reason for not saying that after a single washing enough hexachlorophene might be retained on the cutaneous surface so that during the suc eeding few hours reproduction of the organisms which rema n would be retarded. This retardation of bacterial growth should in turn educe odor

I left the question of retention of bacteria below the electronega tive layer of the stratum corneum unanswered. Your statement that there is also an electropositive layer t about this po nt may be important. Bacteria might be retained just below the barrier zone

DR. LORINCZ The only comment I can make on necrophili of

fungi is that apparently there are a number of substances in the fluid components of the body which are able to inhibit fungi. Among these we have found evidence for a dialyzable, unstable relatively small molecular material. I think Dr. Harvey Blank has recently brought forth evidence for something of the order of a natural antibody or globulin molecule with antifungal activity. Vitamin K might be another such substance. So perhaps there is a host of humoral antifungal substances in the living body which prevent fungal growth in living tissues.

II Circulation and Vascular Reactions

STRUCTURAL ASPECTS AND HEMODYNAMICS OF MICROCIRCULATION IN THE SKIN

BENJAMIN W ZWEIFACH*

Department of Pathology New York University-Bellevue Medical Center New York

The local regulation of blood flow through the peripheral vessels is achieved by the interlocking of several separate systems the sympathetic nervous system local tissue mediators, and factors influencing the intrinsic properties of the vessels themselves (1) It is my purpose, after a brief survey of the general characteristics of the microcirculation in the skin to discuss some recent work dealing with the nature of the chemical mediators concerned with tissue response to injury The minute size of the terminal blood vessels and their extraordinarily delicate nature has made difficult an adequate investigation of their functional activities by any single method of approach The data to be presented have been compiled by three separate experimental techniques. Microscopic observation of the circulation in various laboratory mammals provided a background of information against which it was possible to establish the intimate relationship between structure and function Measurement of various cellular oxidation reduction mechanisms in separate parenchymal and vascular elements in the skin were obtained histochemically by following the *in vitro* reduction of suitable tetrazolium salts in conjunction with selected substrates. The chemical mediators concerned with the reaction of the skin to local injury were studied, by using as experimental models the lesions produced by bacterial endotoxins and vasoactive substances with selected pharmacologic properties

*Established Investigator American Heart Association.

Structural Considerations

Our classical concepts of the manner in which the larger blood vessels subdivide to form the microcirculatory tree have undergone considerable revision in recent years (9). Instead of subdividing repeatedly to form successively smaller arborizations, the terminal ramifications of the arterial and venous vessels exhibit a regular pattern of interconnecting links in association with progressive structural changes in the vessels themselves. The small arteries, as they enter the skin proper, give rise to a series of long arterioles about 50 microns in diameter which, instead of subdividing further, interconnect to form an extensive interarteriolar network. Adjacent links of the arteriolar mesh then give off cross branches, very much like the rungs on a ladder, which approach one another to interconnect by a series of fine capillary vessels. Most of the precapillaries and capillaries, which actually nourish the tissue, are branches of the interarcading arterioles.

In association with the meshwork of large and small arterioles is a comparable series of interconnections between both large and small venules. The prominent venous plexus, which lies in the subcutaneous tissue, is much more extensive than the associated network of arterial vessels. There are significant numbers of direct interconnections between the venous and arterial plexuses, through which blood is shunted back to the venous circulation without traversing the network with capillaries.

The capillary branches immediately below the epidermal layer of the skin are direct offshoots of the interanastomosing arteriolar arcades. Each of the branches is surrounded by several coiled or spirally arranged muscular elements for a short distance before subdividing into two or three capillary loops. These branches are in effect precapillary sphincters, similar to those characteristically seen at this level of organization in other tissues of the bod[illegible] There are occasional capillary branches which arise fr[illegible] eper [illegible] exus and enter the dermis proper [illegible] relatively few in comparison with the [illegible] ber [illegible] branches arising from

the arteriolar arcades, they serve an important function since they continue to supply blood to scattered areas of the skin under conditions where arterio-venous shunts have opened up and are permitting the blood to bypass the majority of skin capillaries.

Functional Behavior

Direct observations reveal a definite intermittency in capillary flow and irregular vasomotor excursions of the deeper arterioles and venules. The small venules of the skin show an extraordinarily prominent vasomotor activity in contrast to other tissues, such as mesenteric structures the wall of the intestinal tract, and skeletal muscle where venous vasomotion is minimal and seemingly passive

As in other structures the muscular components of the terminal vascular bed exhibit a gradient in reactivity which can be demonstrated by determining the threshold concentrations of epinephrine or norepinephrine required to elicit a standard response. Several differences were noted in the skin with respect to other vascular beds. The arteriole to arteriole arcades are exceptionally sensitive to constrictor or dilator agents. As a result of this unusual situation minimally effective stimuli affect principally the arcades and trap blood in the capillary networks. The venular tributaries are highly responsive to changes in temperature to the extent that a fall in temperature of from 1–2 C results in a ten to twenty fold increase in reactivity to epinephrine and norepinephrine Although vascular reactivity fluctuates with temperature in other tissues the venous network in the skin represents a unique structure in this regard.

There is a wide body of evidence to indicate that the small blood vessels of the skin are under the influence of the sympathetic and central nervous system (3 4) Our own group has made an intensive study of the microcirculation in the skin during various forms of systemic and local stress and it is clear that the skin vessel are perhaps the most responsive unit to neurogenic constrictor and dilator influences. During hemorrhagic hypotension for example, the interarcading arterioles

undergo almost complete constriction within minutes after the onset of blood loss and tend to remain narrowed until the blood pressure is restored by transfusion Under these conditions the precapillary vessels shut down so that except for an occasional deep vessel the capillary circulation in the dermis is negligible The underlying network of venules shows a slow but continuous flow chiefly because of direct shunts between the deeper arterioles and venules. With protracted hypotension a considerable backflow develops in the venous plexuses, leading to a reflux into the collecting venules which become filled with stagnant blood The vasoconstrictor response of the skin during stress is mediated for the most part by neurogenic factors since shock induced under spinal anesthesia or in the presence of autonomic blocking drugs, does not result in a comparable curtailment of the skin circulation Actually in the latter cases, the capillary circulation through the skin remains plethoric and slowly stagnates as the shock deepens.

Local Reaction of Skin to Injury

In recent years we have focused attention on the physiological manifestations of bacterial endotoxins (5 6) partly because of the extraordinary scope of their biological properties and partly because the approach provided us with a useful experimental model for analyzing the regulatory mechanisms of the skin circulation It was recognized early that the pathological effect of bacterial endotoxins were closely related to the vascular reactions which they produced (7) Many workers have pointed out that the vascular effects produced by bacterial endotoxin were strikingly similar to those resulting from epinephrin (8,9) It has been shown that the necrotizing action of bacterial endotoxins in the skin of rabbits could be reproduced by various combinations of epinephrine and endotoxins (3) For example the conventional Shwartzman skin lesion is elicited in the rabbit by two appropriately spaced injections of bacterial endotoxin the first in the skin and the second provocative dose intravenously about 18 to 20 hours later Extensive dermal necrosis and hemorrhage can be produced by the administra

tion of endotoxin systemically and the local injection of epinephrine into the skin. Mixtures of epinephrine and endotoxin injected into the skin likewise lead to a hemorrhagic lesion despite the fact that epinephrine by itself, even when injected repeatedly for periods up to 6 hours into a given skin site, did not produce a comparable lesion (10).

Direct observations of the circulation in the skin have revealed that the Shwartzman type of lesion is accompanied initially by an exaggerated response of the small blood vessels to epinephrine and norepinephrine (6). Thus, normally threshold doses of epinephrine produce in the endotoxin treated animal protracted vasoconstriction, and when repeated several times lead to capillary stasis and tissue damage. We were interested in this lesion because it involved two separate aspects of local homeostasis. First, there was evidence of an altered attitude of the smooth muscle cells to vasoconstrictor agencies, particularly the catechol amines; and secondly, the extensive curtailment of local blood flow was accompanied by endothelial damage, as manifest by capillary stasis and petechial hemorrhages. Direct visual studies revealed that the altered pattern of reactivity involved not only the feeding arterioles but also the effluent venules. The reactivity of the venules after endotoxin was heightened to the extent that a threshold stimulus which normally produced a transient effect lasting at most 1–2 minutes, in the endotoxin treated animal resulted in an unrelieved narrowing of the venules which persisted with a single dose of epinephrine for as long as 45–60 minutes. Subsequently the reactivity pattern, particularly on the arterial side, shifted toward a diminished response until the feeding arterioles were fully dilated.

One of the working hypotheses advanced to account for the changes in the skin circulation was the possibility that during tissue damage there was an interference with the inactivation of epinephrine, as a result of which local concentrations of epinephrine were kept at high levels. Such a mechanism would account for the increased response to epinephrine as well as the tendency of the smooth muscle elements of the venules to remain constricted when stimulated. Inasmuch as there was no

definite evidence in the case of bacterial endotoxins that these materials acted directly on the blood vessels the possibility was explored that the endotoxins brought about a release of other amines which either interacted synergistically with local epinephrine or norepinephrine or which competed with epinephrine for its inactivating enzyme For many years it was believed that the enzyme concerned with the regulation of epinephrine was monamine oxidase More recently it has been shown that this enzyme system is probably concerned chiefly with the inactivation of another amine, serotonin or 5-hydroxytryptamine (11) Since 5-hydroxytryptamine has a widespread distribution and has been shown to be released during various forms of stress and tissue damage this potent vasoactive agent might conceivably represent the hypothetical competitor of epinephrine which our concept required

5-Hydroxytryptamine in Local Skin Reactions

Several separate lines of investigation have supported the importance of 5-hydroxytryptamine as a mediator in the local skin reactions to bacterial endotoxins and to tissue injury in general again within the framework of the epinephrine reaction as the central figure of these conditions.

Although neither 5-hydroxytryptamine nor epinephrine by themselves leads to local tissue damage mixtures of the two amines produce dermal necrosis and extensive capillary hemorrhage (12) These lesions are almost indistinguishable from those produced by endotoxin and epinephrine Direct observational studies of the microcirculation in the skin revealed that a mixture containing threshold amounts of both of these agents when administered repeatedly produced extensive damage to the capillary endothelium and of particular interest the characteristic venospasm in the effluent venules These experiments suggested that tissue damage was associated with the local release of 5-hydroxytryptamine or some associated humoral mediator It is well known that vasoactive substances can originate in particular components, such as the mast cells which accompany the small blood vessels and which are unusually prominent

in ectodermal structures. There also exists in the literature a wide array of chemical substances which have been termed histamine liberators (13) so named because they were shown to bring about the disruption of mast cells and blood platelets and the freeing of histamine from its bound form in association with tissue polysaccharides. More recently it has been shown that most of these liberators also bring about the release of other pharmacologically active substances including 5-hydroxytryptamine, various esterases, and heparin (14) The substance 48/80 has been widely used and was selected for experimental study since in the dosages employed it could be shown to have little or no effect on other systems

Effects of Compound 48/80

The local injection of 48/80 in extremely small amounts (in the rat as little as 10–8 gamma) produces a local wheal the development of which was measured either by the exudation of intravenous dye or by the outward passage of albumin labeled with an iodine isotope. It is of interest in this regard to note that the skin lesions produced either by endotoxin or by epinephrine and endotoxin or epinephrine and 5-hydroxytryptamine or 48/80 can be circumvented by the use of autonomic blockading drugs, especially those which interfere with both epinephrine and 5-hydroxytryptamine. Among these drugs are agents such as dibenzyline chlorpromazine and Phenergan

One further possibility was explored namely the use of repeated administration of 48/80 as a means of depleting the skin of its available stores of vasoactive intermediaries. This end was achieved by giving small doses of 48/80 to rats at daily intervals for periods of 3–5 days. The skin could then be shown to be free of histamine or 5-hydroxytryptamine by bioassay procedures. If our hypothesis is correct concerning the importance of these vasoactive substances in tissue injury such pretreatment should significantly alter the reaction in the various experimental models under discussion. Such was actually the case. The local skin reaction to the various mixtures of endo-

48/80 is condensation product of alkophenylalkylamine and formaldehyde prepared by the Burroughs Wellcome Research Laboratories.

toxin epinephrine and 5-hydroxytryptamine were almost completely wiped out in animals pretreated with 48/80

Interestingly enough this form of pretreatment not only altered the subsequent reaction of the skin to tissue injury but also permitted animals to survive otherwise lethal traumatic or hemorrhagic shock When bacterial endotoxins are given systemically they produce various pathological manifestations, including generalized tissue injury involving the blood vessels of the kidney and small intestine and with large single doses *an acutely lethal syndrome Here again the toxic and lethal* sequelae could be circumvented by pretreatment with 48/80 Another interesting observation was made in the skin of rats subjected to trauma in the rotating Noble Collip drum Normal controls when exposed to large doses of trauma by this means show extensive petechial hemorrhages and hematoma in the skin. Animals which had been depleted with 48 80 prior to exposure to drum trauma showed no evidence of petechial or capillary damage in the skin pointing to a protective action against the direct effects of tissue injury

Summary and Conclusions

The above studies have led us to conclude that we are dealing in the case of the skin circulation with a set of tissue mediators, either directly through 5-hydroxytryptamine or through an effect resulting from the local accumulation of this substance in the tissue The suggestion has been advanced that the reaction involves also the local release of either epinephrine or norepinephrine and hence is probably dependent upon neurohumoral factors. The so called depletion experiments with 48 80 although corroborating the important role of these amines in local tissue homeostasis, may involve indirectly other tissue mechanisms, possibly concerned with an adaptation to the repeated release of vasoactive agents

REFERENCES

1 Zweifach B W Basic mechanism in peripheral vascular homeostasis *In* to *Regulating Blood Pressure T a Third*

Conference Josiah Macy Jr Foundation New York 1919
2 Zweifach, B W General principles governing the behavior of the microcirculation *Am. J Med* 23 681 (1957)
3 Kerslake D McK., and Cooper K. E. Factors concerned in the regulation of skin blood flow *Peripheral Circulation in Man Ciba Foundation Symposium* Little Brown & Co Boston 1954
4 Lewis, T *Blood Vessels of the Human Skin and Their Responses* G Shaw & Sons, London 1927
5 Zweifach, B. W Nagler A L., and Thomas, L. The role of epinephrine in the reactions produced by the endotoxins of gram-negative bacteria. II The changes produced by endotoxin in the vascular reactivity to epinephrine in the rat mesoappendix and the isolated, perfused rabbit ear *J Exptl Med* *104* 881 (1956).
6. Zweifach B. W and Thomas, L. The relationship between the vascular manifestations of shock produced by endotoxin trauma and hemorrhage. I Certain similarities between the reactions in normal and endotoxin-tolerant rats. *J Exptl Med* *106* 385 (1957)
7 Delaunay A., and Lebrun J Le mode d action des endotoxines bactériennes. II Les troubles circulatoires chez les animaux intoxiqués par une endotoxine. *Ann inst Pasteur* *73* 565 (1947).
8. Delaunay A Boquet, I Lebrun, J Lehoult, Y and Delaunay M Le mode d action des endotoxines bactériennes les troubles vasomoteurs chez les animaux intoxiqués et leurs conséquences. *J Physiol (Paris)* *40* 89 (1948)
9 Thomas, L. Bacterial endotoxins. *Ann Rev Physiol* *16* 467 (1954)
10. Thomas, L. The role of epinephrine in the reactions produced by the endotoxins of gram-negative bacteria I Hemorrhagic necrosis produced by epinephrine in the skin of endotoxin-treated rabbits. *J Exptl. Med* *101* 865 (1956)
11 Blaschko, H Amine oxidase and amine metabolism *Physiol Revs* *4* 415 (1952)
12 Thomas, L., Zweifach B. W d Benacerraf B Mechanisms in the production of tissue damage and shock by endotoxins. *Trans. Assoc Am Physicians* 0 51 (1957)
13 Paton, W D M Histamine release by compounds of simple chemical structure *Pharm Revs* 9 269 (1957)
14 Sparrow E M and Wilhelm D L Species differences in susceptibility to capillary permeability factors histamine, 5-hydroxytryptamine and compound 48/80 *J Physiol (London)* *137* 51 (195).

Discussion

Dr. Stoughton I would like to ask Dr Zweifach whether the changes he observed with norepinephrine and serotonin were similar histologically to those of the Shwartzman reaction. And if they are has he done anything in relation to obliterating the reaction with nitrogen mustard or other methods that have been used to obliterate the Shwartzman reaction the idea being that they are dependent upon antibodies rather than on just epinephrine or serotonin?

Dr. Zweifach The problem of whether or not the Shwartzman reaction involves antibodies is controversial. Even if we were to accept this premise, there remains the question of the mechanism by which an antibody-antigen reaction results in vascular damage. This problem represents the primary area which we were trying to resolve. *There is some evidence that the mediation of the damage* inflicted by the antigen antibody reaction involves the mechanisms under discussion. On the basis of histopathology the dermal necrosis, produced by epinephrine and endotoxin combinations, is very similar to that produced in the conventional Shwartzman. Mixtures of epinephrine and serotonin produce a local skin reaction without extensive infiltration of white blood cells characteristic of the endotoxin-prepared site Thomas conducted experiments with nitrogen mustard and found that the leucopenia did not prevent the epinephrine 5-HT lesions.

Question How about the role of cellular infiltration?

Dr. Zweifach I don t think the cellular infiltration is an essential preparative feature of the dermal necrosis induced by mixtures of amines.

Dr. Rothman Dr Stoughton, you and Dr *Zweifach* are talking at different levels. You are talking about inhibiting the antibody formation while Dr Zweifach implies that the antibody-antigen reaction ends with the liberation of some biogenic amines. It was proposed until now that the immediate urticarial reaction i the result of an antigen-antibody reaction which ends with the libera tion of h stamine

Dr. Zweifach I think that histamine has been emphasized without due consideration to other amines uch as 5-hydroxytryptamine It is most intriguing to consider that the essel in a skin depleted of its mast cells, amines, norepinephrine et by so-called histamine liberators react differently to all sort of traumatic episodes than does the normal untreated skin. This is a challenging situation. We are uncertain whether the altered reactivity is due to the depletion per se or whether it is associated with some other *ancillary effect* dependent upon repeated release of these ubstances and a subsequent adaptation.

PHYSIOLOGY OF CUTANEOUS CIRCULATION THERMOREGULATORY FUNCTIONS

ALAN C. BURTON

Department of Biophysics, University of Western Ontario, London Ontario

I propose to discuss the physiology of the circulation of the skin in a very teleological manner In my opinion teleology is a most useful almost essential tool of thinking for the biologist. The fact is that consistent useful patterns do appear in nature, and I can see little to quibble about saying that this or that feature exists in order to fulfill some physiological need or to say that it serves that particular function " as long as we remember that everything does not work out to the advantage of the animal. The best laid physiological plans of mice and men go often astray when unusual environmental or internal bodily conditions are encountered A control mechanism, however well adapted to meet the average operating conditions, cannot be expected to work well in all possible circumstances, as we well know Anyway I know no way of making learning and remembering easy as good as the judicious use of teleology with reservations and caution.

Let us then discuss the purpose of circulation in general, and its physiological control in general and for the circulation of the skin in particular I shall then outline briefly and sketchily what we know about some peculiar characteristics of the skin circulation and how it serves that purpose Finally we may discuss the mechanisms that may exist for meeting unusual circumstances outside the average physiological conditions, in the control of skin circulation This is in the hope that some light may be shed on what is encountered in dysfunctions of the skin and their treatment.

The Purpose of Circulation

In general the purpose of circulation is to supply oxygen and nutrients to every cell in the organism and to remove the unwanted end products of the living activity of these cells. Most cells are completely dependent on the circulation for these functions but there are a few *exceptions* *The cells of the pulmonary alveolae* do not depend at all on the circulation for oxygen nor for removing CO_2 and water direct diffusion of gas suffices. To some extent this is true of the cells of the skin particularly the outermost layers. It is undeniable that the skin of a limb deprived of circulation will change color toward the pink of oxygenated tissue when that limb is surrounded by pure oxygen There is evidence also that atmospheric oxygen *so absorbed by the skin can actually be utilized* in cellular metabolism I was intrigued many years ago when some colleagues [Goldschmidt *et al* (1) at the University of Pennsylvania] sealed naked subjects in a large metal can up to their necks, and measured their BMR by a metabolism machine from which they breathed They were able to show that when the can was full of O the O consumption by the mouth was significantly lowered below the value measured when the can was full of N_2. However the difference was only a very few per cent and would be correspondingly less with the partial pressure of O in air However in cases where death of skin is threatened by ischemia we should remember this possibility If we were to lower the metabolic needs of the skin by cooling to a low temperature it is entirely possible that direct diffusion from an atmosphere of pure O might tip the scales toward survival of these skin cells.

Need for Control of Circulation

For an ideal bodily economy one would suggest that the circulation should supply O and remove end products to each cell *in accordance with the needs of that particular cell* There is an enormous range of relative requirements of the cells of different tissues At the top of the range stands the kidney then

some of the cells of the central nervous system of which the retinal cells are quoted as requiring most then the muscles and liver At the bottom of the scale stand the cells of bone, the cornea and so on The cells of the skin are very low in the list. From the available literature (9) mostly from the results of *in vitro* technique (and jumping from rat to man) I made a very rough estimate of the minimum requirement for the cells of skin as supplied by about 0.8 cc of blood flow per minute per 100 cc of skin tissue (3) This is very low and evidently even in prolonged general vasoconstriction as in the cold, the blood flow of the skin suffices for this. I have not heard of pathology of skin developing in such vasoconstriction even for days, though curiously enough some climatic experiments in the cold have shown such pathology to develop *after* the subjects returned to warm surroundings.

The needs of various tissues for O_2 differ also in their range of variability The brain cells have a large but apparently quite constant requirement for extra physiological activity of the brain does not involve extra O_2 consumption In contrast muscle in its activity of contraction needs a great deal more oxygen (up to 20 times) and hence correspondingly more circulation than when at rest In the case of the skin the requirement would not be very variable, the chief factor being the skin temperature. From the usual Arrhenius law of increase in activity of chemical reactions with temperature we would estimate perhaps a sixfold variation in the usual range of skin temperature

All this would suggest that in addition to distributing blood flow in different amounts to the different kinds of tissue the circulation must cope with the very great changes in requirement of some tissues at different times, i e there must be a rather elaborate automatic or reflex control of the circulation. I wish I had time to remind you of the wonderful way the controls of circulation that we know deal with this problem For example the constant and large requirement of the brain tissue is provided by a constant head of pressure at the portals of the brain ensured by the carotid sinus reflex together with a relatively fixed resistance to flow of the brain vessels, which

are largely lacking in vasomotor activity In contrast the enormous increase in requirement for *circulation of the muscles in* exercise are met by the dilation of muscle vessels to adrenalin secreted and circulating in heavy exercise and by the local control of "reactive hyperemia elicited by CO_2 and lactic acid so well studied in muscle by Barcroft and his colleagues (4)

With these considerations in mind let us look at the amount and variability of the circulation of skin to see how it fits the metabolic requirements, and the range of requirement.

Range and Variability of Skin Circulation

I could discuss this in great detail for we know many facts about it, but unfortunately about only one type of skin that of the digits This is because of the fortunate circumstance for the physiologist that the blood flow of the digits is almost entirely to skin there being no muscle present and the bone flow being negligible The blood flow of the digits is easily measured by the venous-occlusion plethysmograph (5) in cubic centimeters per minute per 100 cc tissue and thousands of measurements in all sorts of circumstances have been made by many other laboratories as well as mine Unfortunately we know that the features of the circulation of skin elsewhere are *not the same as in the digits indeed in some areas the characteristics* are in direct contrast We know far less of the skin circulation in the other regions mainly because only indirect methods, such as skin temperature oscillometry of the skin and calorimetry are available I managed once to do plethysmography on my own ears, enough to learn the contrast in behavior with my fingers I shall emphasize some of these regional differences by the little we know about them

What is found for the skin of the digits I will summarize very briefly

First the range is from a minimum of about 0.5 to 1.0 cc/min/100 cc tissue in full vasoconstriction to a maximum in full vasodilation obtained with the subject uncomfortably hot and *sweating of over 90 cc min 100 cc tissue* Even higher maximum values have been found in acclimatization to heat In one

case of a subject living in a hot room (32.4° C, 112.3° F) the maximum increased in five days from 96 to 199 cc/min/100 cc tissue (admittedly the plethysmographic measurements become very rough with these very high flows). On the return to living in a cool room the minimum value decreased in three days from 16 to 1.8 cc/min/100 cc (5). The range is therefore at least one hundredfold, and the limits shift with climatic adaptation.

Secondly the finger blood fluctuates remarkably from moment to moment. It is quite easy to repeat measurements of flow every 6 seconds. From a long succession of these the standard deviation about the mean flow of the whole period can be obtained. It turns out that this is as high as ±20% in the middle of the range of blood flow. It is much less at the ends of this range, i.e., in sustained vasoconstriction or sustained vasodilation.

Before we consider the mechanism of this enormous range and variability let us see how these facts fit into the ideas, about need for control of circulation that I have suggested above. It seems quite clear that neither the great range, nor the fluctuation from moment to moment are consistent with control of the skin circulation (at least of the digits) in accordance with the needs of the skin cells. The minimum blood flow found would suffice for the needs of these cells, unless the skin temperature were very high. The range is far in excess of any change in requirement for blood flow of skin and there is no fluctuating need of skin cells that would explain the remarkable variability from moment to moment.

Function of Vascular Control in the Skin

Thus the control of blood flow of a digital skin is not in the service of the skin itself but to serve a function or functions for the whole organism. The main purpose is easily seen to be in temperature regulation. This was evident when we investigated the details and the mechanism of the continual fluctuation. The small blood vessels of digital skin, i.e., the arterioles, are apparently always in a transitory state either of constriction or of dilation, or in the course of changing from one to the

other Records of the finger volume pulse which was shown in the particular experimental conditions to be very well correlated with the blood flow revealed that there was a rhythm of vasoconstriction from as many as ten a minute in full vasoconstriction to one only every 5 minutes in full vasodilation The frequency of recurrence of vasoconstriction depends on whether the subject was warm or cold and the mean period between vasoconstrictions was dependent on the environmental temperature (6) The constrictions were simultaneous in toes and fingers, and so many vessels in the body were constricting simultaneously that the arterial blood pressure transiently rose at the same moment

It was shown that these widespread periodic vasoconstrictions in the skin vessels were mediated by impulses in the sympathetic system The heart rate increased simultaneously so there is a mass discharge in that system In a sympathectomized limb the correlation with the innervated areas was completely absent Further experiments in water baths at different temperatures showed how effectively the modification of this rhythm in the *sympathetic vasoconstrictor system in the interest of temperature regulation* adjusted the mean skin blood flow to a value appropriate to the required heat loss from the extremities. Thus we felt we understood the mechanism by which the sixfold change in effective insulation of the tissues (7) found in previous experiments had been brought about These large changes in the insulation of the whole immersed body suggest that the control of skin flow for temperature regulation is not confined to the skin of the digits. Indeed data on skin temperatures over the trunk as well as the extremities in different environmental temperatures (8) show that the control of skin flow for this function is widespread though the range of control is not great elsewhere as it is in the digits.

Differences in Different Skin Areas

It has long been known that the very great changes in skin flow in the digits and in the rabbit ear (9) are brought about not only by vasomotor control of the arterioles controlling the

capillary beds, but also by the unique "arterio-venous shunts" found in these locations (but not yet definitely shown in other areas of skin) Latex and plastic injection casts of these have been beautifully demonstrated by Daniel and Pritchard (10) in the ears of rabbit and sheep These shunt the blood directly from artery to vein bypassing the resistance offered by the capillary bed and increasing the flow enormously It is of great interest that Hurley and Mescon (11) have recently shown by histochemical staining that the myoepithelial cells of the glomus body of these shunts is heavily innervated cholinergically Again the point can be made that the operation of these shunts is not in the interest of the skin itself but of the whole organism Kety (12) and others, using the technique of radioactive clearance have shown that the increased flow through these shunts does not, as does capillary flow increase the diffusion from blood to tissues. This is an important point for the dermatologist, for some of his therapeutic measures conceivably may increase the skin flow mainly by opening the shunts. If so there will not be a corresponding increase in the nutrition of the skin cells.

While the major role of these arterial-venous anastomoses is in temperature regulation a second function may be suggested once more in the service of the whole organism rather than of the skin. Similar shunts exist in abundance in the stomach and mesenteric circulations (13) where they can play no conceivable part in temperature regulation They seem to open and close more or less automatically A violent closure of the capillary bed as to a circulating vasoconstrictor agent or to some local stimulus, results in their opening Indeed we have suggested a biophysical theory of operation of all such arterial venous shunts (14) with supporting evidence from work on the digits. It may well be that the shunts act like the safety valves on a boiler a violent rise of blood pressure brought about by intense vasoconstriction elsewhere raises the pressure in their lumina and automatically open them preventing an excessive rise of pressure This is pressure regulatory rather than thermoregulatory and may be one of the functions of the skin that is not usually listed.

We know that one area of skin differs greatly from the rest in the physiology of control of its blood flow *This is the skin of* the head neck and upper thorax the so-called blush area It is well known that inhalation of amyl nitrite a general chemical dilator of blood vessels produces a profound flushing of this area. Many other vessels also dilate, for the blood pressure tends to drop precipitously Yet we found that simultaneously with the increased blood flow of the skin of the blush area there is a strong vasoconstriction in digital skin (15). That region of the skin is dominantly under the control of the nervous system and the carotid sinus reflex, elicited by the fall in blood pressure would account for the clamping down of the digital vessels—an example of the pressure regulatory function of the skin In the case of the skin of the blush area there *is very little if any vasomotor control so chemical effects are* unopposed whereas in the digits the nervous effects completely overshadow the chemical We recently verified this vasomotor inactivity of the skin of the head and neck in a research on the heat losses of the head (16) This shows no sign of taking part in the thermoregulation of the rest of the body In a cold environment the thermal insulation of the fingers increased six times over that in the warm yet the thermal insulation of the head did not change at all

Autonomy of Skin Blood Flow

Though my main point has been that the control of skin blood flow is dominated particularly in the case of the extremities, by the needs of the whole organism there are some mechanisms by which skin flow is regulated in accordance with local needs. These are nothing like as important as in muscle where local control is dominant I know of three such mechanisms.

REACTIVE HYPEREMIA

Dr Patel and I (1) recently measured reactive hyperemia in the fingers, where the continued fluctuation makes it difficult *to distinguish the underlying trend* Thus we eliminated by using a second finger as control and since the fluctuations are

completely correlated, using the difference between control and previously occluded finger. There is, however, no consistent relation of the amount of the extra blood flow after deprivation to the amount of the oxygen debt, the duration of the period of occlusion and so on as there is in muscles. In fact, since the requirements of skin are so minimal, the excess flow is far greater than the blood flow debt. There is also evidence that if the deprivation of blood flow is accompanied by venous distention as when there is venous obstruction, constrictor effects may be elicited in what we have called a local veno-vasomotor reflex (17). Because of this reflex, posture of the limbs greatly influences their skin circulation. While undoubtedly this type of autonomous local control, i.e. reactive hyperemia of tissue blood flow exists in the skin and probably operates in disturbed physiology as in local inflammation, it is not as simple and straightforward a mechanism as in other tissues.

COLD VASODILATION: THE "HUNTING REACTION" OF LEWIS

We have continued to investigate this curious phenomenon in the skin of the fingers. When a finger is immersed in cold water there is a progression into intense vasoconstriction, the skin temperature falls almost to freezing temperature and there is considerable pain. Suddenly after 4 to 5 minutes there is a local and very great increase in blood flow, the pain is relieved and the finger feels very warm, even though its skin temperature, which has risen considerably, is still less than that of adjacent fingers not immersed. This is succeeded by a second sudden vasoconstriction, and constriction and dilation follow each other in cyclic fashion as long as the experiment continues. There has been a great deal of research on this, notably by Greenfield and his associates (18), but its mechanism remains rather mysterious. As the very large increase in flow in cold vasodilation is known to be largely due to the opening of the shunts, the capillary flow may not be correspondingly increased. However, the increased flow, shunt flow or not, does result in a warming up of the tissues and thus has a local protective function against freezing. This is at a considerable disadvantage to the total thermal economy of the organism against cold, for the

heat loss in this vasodilation from the digits alone would amount to a great deal We are inclined to think of this phenomenon as a curiosity and a physiological accident rather than a protective adaptation in the interests of the skin tissues.

ELASTICITY OF THE SKIN CIRCULATION

The blood vessels of the skin have a remarkable power of regeneration and increased vascularity in response to abnormal conditions that represents a very important local autonomy To use only one example with which I am familiar Heroux (personal communication) recently examined histologically the vascularity by capillary counts per unit of tissue in the ears of rats After exposure to cold for several days, the vascularity in the skin shows a most remarkable increase This seems to be the chief autonomous regulation of the skin circulation and of great importance in considering dysfunctions of the skin Use of the trophic stimulus of cold to produce increased vascularization is worth considering in therapeutics of the skin

Conclusion

This brief survey of the physiology of the circulation of the skin I hope will lead to the generalization with qualifications, that in its blood flow the skin is peculiarly the servant of the whole organism and is less endowed with autonomous control than other tissues. Possibly this view is important in understanding the susceptibility of the skin to ischemia in abnormal conditions, and worth remembering in considering management of disturbed skin function

REFERENCES

1 Goldschmidt, S M Clone B and Donal J S O bsorption through the skin *Am J Med Sci* 18? 58? (1931)

2 Hell J Belding, H S and Martin A W Relation between basal metabolism and summation of excised tissue metabolism in young albino rats. *Am J Physiol* 1?? (1938)

3 Burton A C The range and variability of the blood flow in the human finger *Am J Physiol* 127 437 (1939)

4 Barcroft H and Swan, H J C *Sympathetic Control of Human Blood Vessels.* E. Arnold, London Williams and Wilkins, Baltimore, 1953

5 Burton, A C., Scott, J C. McGlone B and Bazett, H C. Slow adaptations in the heat exchanges of man to changed climatic conditions. *Am J Physiol* 129 84-101 (1939)

6. Burton, A. C., and Taylor R. M A study of the adjustment of peripheral vascular tone to the requirements of the regulation of body temperature. *Am J Physiol. 129* 565 (1940).

7 Burton, A. C., and Bazett H C. A study of the average temperature of the tissues, of the exchanges of heat and vasomotor responses in man by means of a bath calorimeter *Am J Physiol. 11* 36 (1936)

8. Burton A C. The application of the theory of heat flow to the study of energy metabolism. *J Nutrition 7* 497 (1934)

9 Grant, R. T and Bland E. F Observations on arteriovenous anastomoses in human skin and in the bird's foot with special reference to the reaction to cold. *Heart 15* 385 (1931).

10 Daniel, P M and Pritchard M M L. Arterio-venous anastomoses in the external ear *Quart J Exptl Physiol. 41* 107 (1956)

11 Hurley H J Jr and Mescon H Cholinergic innervation of the digital arterio-venous anastomoses of human skin A histochemical localization of cholinesterase. *J Appl. Physiol 9* 82 (1956)

12 Kety S. S Measurement of regional circulation by local clearance of radioactive sodium. *Am Heart J 38* 321 (1949).

13 Walder D N Some observations on the blood flow of the human stomach, in Ciba Symposium *Visceral Circulation* Churchill Ltd., London, 19 — Page 210

14 Burton, A. C., and Eagan C. J The operation of arterio-venous anastomoses and the "hunting reaction" of Lewis. *Proc of 20th Intern Congr Physiol* Brussels, 1956 Page 150.

15 Burton A C. The blood flow temperature and colour of the skin in *Blood Heart and Circulation* American Association for the Advancement of Science, Washington, D C., 1940 Page 308

16. Froese, G and Burton, A. C The heat losses of the human head. *J Appl Physiol 10* 235 (1957).

17 Patel D J and Burton, A C Reactive hyperaemia in the human fingers *Circulation Research 4* 710 (1956).

18 Greenfield, A D M Shepherd, J T and Whelan R. F The loss of heat from the hand and from the fingers immersed in cold water *J Physiol (London), 11* 159 (1951).

Discussion

Dr. Sid Robinson (University of Indiana) What are the actual blood flow relationships in the hunting phenomenon of Sir Thomas Lewis in these periodic vasoconstrictions and vasodilatations?

Dr. Burton The plethysmographic method for determination of blood flow does not work during the phases of intense vasocon striction Evidently the veins are so constricted that there is no reservoir into which blood can pile and thus increase the volume of the finger before it reaches a pressure so high that it slips by Instead of getting a plethysmographic curve which rises and then flattens so that the initial tangent can be determined it just rises in one beat and stays there. As far as I know no one has yet been able to measure blood flow plethysmographically in this circumstance. Such flow measurements when attempted are usually made calorimetrically We measured the heat coming from the finger and so did Green feld. Judging from the heat that comes off blood flow is higher dur ing the periods of vasodilation than you get with any other kind of vasodilation Dr Robinson have you succeeded in getting meas urements plethysmographically? Evidently all the shunts are open and, during these cycli periods of vasodilation, one gets a blood flow that compares witl the blood flow one gets by heating a man and making him uncomfortably hot.

Dr. Rothman As concerns these sympathetic rhythmic intrinsic impulses running from the central nervous sy tem to the periphery ll the environmental temperature changes, ap parently the frequency of these imp ulses changes. I this a reflex and, f so what k nd of afferent pathw ys do you a ume to function here? Are they sympa thetic runn ng up ward or are they sensory?

Dr. Burton The same question occurred to us as soon as we found this phenomenon Dr Taylor and I did a pretty thorough study to find out whether the rhythmic changes of skin temperature produced the afferent impulses for the next vasoconstriction By studying the phenomenon in well-stirred water where the skin tem perature s not allowed to change and finding that the rhythm wa just the same we ruled out this possibility I think that like many other central nervous system ells, those of the hypothalamus are intrin ically rhythmic in sending out these sympathetic impulses and the rhythm i modified by the afferents coming to the temperatur regulating center In other words, t is not the cyclic afferent which produce the next vasoconstriction but rather there is a modification of an intrins rhythm

M Edward our l borat ry has now suc eeded The lues sim ilar to those f und n other types of soconstrictio nd asodilation

PATHOLOGY AND THERAPY OF CUTANEOUS CIRCULATORY DISORDERS

ROBERT R. KIERLAND

Section of Dermatology, Mayo Clinic and Mayo Foundation
Rochester, Minnesota

In the consideration of cutaneous circulatory disorders one must begin by defining this term. A moment of thinking will indicate that there are extremely few, if any, dermatologic conditions that do not result from, include, or provoke some vascular alteration either anatomic or physiologic. Obviously in the brief scope of this presentation one cannot begin to cover the subject thoroughly. The application of the phrase "cutaneous circulatory disorders" therefore will be limited to those acquired, nontraumatic, nonmalignant cutaneous afflictions produced by primary anatomic or physiologic alterations of blood vessels. By such definition are excluded diseases of lymph vessels, congenital abnormalities such as hemangiomas and arteriovenous communications, angiosarcomas, anemias, purpuras, abrupt arterial occlusions, aneurysms, new growths, and vascular disorders without dermatologic manifestations. Still the list to be included is too long. As a result, certain important entities have been excluded arbitrarily: lupus erythematosus, nodular vasculitis, allergic vasculitis, periarteritis nodosa, and others. In fact, we do not know whether vascular alterations produce the dermatologic signs and symptoms or whether the process is reversed in many of these conditions.

In the preparation of the basic material I have drawn freely from the books of Ormsby and Montgomery (1), of Pillsbury

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Shelley and Kligman (2) of Rothman (3) of Allen Barker and Hines (4) and of Wolstenholme and Freeman (5) Later in the paper suggested avenues of further physiologic investigation will be considered. To this audience of primarily basic scientists, the anatomic, physiologic and pathologic considerations are most important however I have been asked to discuss the pathologic clinical and therapeutic aspects of cutaneous circulatory disorders, and these I have categorized according to the basic pathologic condition of the blood vessels involved

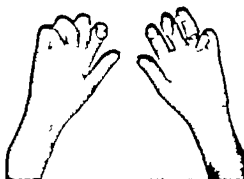


Fig 1 Raynaud s phenomena in association with scleroderm showing punctate ulceration nd scarring

Conditions Associated with Arterial Constriction

First is a group f conditions in which vasoc nstricti n of the arterial side of the circulation appears t be the primary pathologic change Raynaud s disease and Raynaud s phenomena livedo reticularis and probably acrocyanosis are the m st prominent clinical examples of this group

RAYNAUD S DISEASE AND PHENOMENA

The nly clear cut distincti n betw een Raynaud disease and Raynaud s phen mena is that in the f rmer there are no frank associated findings The clini al findings of th e acra in the disease are triggered by c ld and by em ti nal timuli a with Raynaud s phenomena With Raynaud s phenomena h wever

are associated such findings as evidence of trauma occlusive arterial disease neurologic lesions, and miscellaneous states such as systemic lupus erythematosus paroxysmal hemoglobinuria and scleroderma (Fig 1) Actually many investigators prefer to speak of Raynaud's phenomena only avoiding the word "disease by use of the qualifying terms primary and secondary"

In this condition the classic color changes of pallor cyanosis, and rubor following emotional upheavals or exposure to cold involve first the finger tips and afterwards may spread proxi



FIG. 2. Severe and extensive gangrene as a consequence of intense Raynaud's phenomena of the secondary type in a patient with scleroderma.

mally Later still the toes, hands, tip of nose and ears may become involved. Extensive gangrene does not occur with the primary phenomena or Raynaud's disease small punctate areas of gangrene at the finger tips and the toes occur infrequently in patients with disease of long duration Gangrene may be extensive with Raynaud's phenomena of the secondary type (Fig) This condition usually appears in women in the third and fourth decades of life In most patients with mild but yet chronic Raynaud's phenomena gangrene may never develop because the episodes are of short duration By some this is called functional vasoneurosis.

Most authorities seem agreed that the findings described are due primarily to vasospasm of the digital arteries, but disagree as to what initiates this vasospasm Some believe that the fault is local while others think that it lies with the vasomotor nerves.

Practically nothing is known of the early pathologic state of the digital arteries. As the condition becomes chronic and advanced the intima of the arteries becomes thickened

Treatment obviously is directed toward prevention of vasospasm by both surgical and nonsurgical methods. Avoidance of smoking of cooling and of emotional tension stress and strain



FIG. 3 Livedo reticularis (infrared photograph).

is essential and in milder cases is sufficient to prevent further development of Raynaud s phenomena In other cases the administration of vasodilating agents may prove of some value although as a rule nonsurgical management is unsatisfactory If the Raynaud s phenomena are of the secondary type relief or cure of the underlying disorder is most important Sympathectomy is the most satisfactory treatment of Raynaud s disease but sympathectomy alone will not necessarily alter the course

of underlying disease in secondary Raynaud's phenomena—for example sympathectomy in a patient with scleroderma will have no effect on the progression of the cutaneous sclerosis or its associated internal findings.

LIVEDO RETICULARIS

Another vasospastic disorder livedo reticularis, is featured by blotchy or reticulated red or bluish red markings in the skin most prominent about the ankles and legs, less prominent on thighs, buttocks and forearms It occurs usually in women (Fig 3) The eruption ordinarily is more apparent in cold weather although there is a small group of patients (6) in whom the livedo is more apparent in summer and is associated with



Fig. 1 Livedo reticularis with ulcerations of small infarctive type.

small infarctive ulcerations about the ankles and lower portion of the legs (Fig 4)

The cause of livedo reticularis is obscure. Hypertension as well as nervous instability has been noted as a frequent accompaniment. Associated cryoglobulinemia rarely is seen In one of my patients with the summer ulcerative type serious systemic lupus erythematosus developed after the ulcerations had been controlled well by the administration of hexamethonium

The physiologic changes studied in livedo reticularis indicate predominance of vasospasm of the arterioles with dilation of

the capillaries and venules. The obstruction affects only the arterioles occurring peripherally thus accounting for the reticulated discoloration Microscopic study of involved tissue reveals intimal proliferation of arterioles and small arteries and in some cases thickening of the muscular wall Occasionally there is complete occlusion of the lumen

Treatment is not necessary in the great majority of cases since the only complaint is a cosmetic one In severe instances and in those associated with recurrent ulceration either summer or winter sympathectomy has been advised More recently my colleagues and I have had success with nonsurgical measures alone namely the use of antihypertensive agents such as hexamethonium or pentolinium (ansolysen)

ACROCYANOSIS

In the past acrocyanosis has been confused with Raynaud's disease It occurs as a persistent blueness in the fingers and hands and to a lesser degree the toes and feet of girls and young women Constant coldness of the acra and frequent hyperhidrosis are associated Although worse in cold weather the symptoms do not disappear with warmth Occasionally acrocyanosis may be the first manifestation of lupus erythematosus. Evidence of occlusive arterial disease is not present and atrophic changes do not occur

The exact physiologic mechanism at fault is uncertain Seemingly there is a strong sympathetic influence resulting in heightened arteriolar tone and arteriolar spasm followed by secondary dilation of the capillaries and venules.

Treatment usually is not necessary except that as in all cases of vasospastic disorder cold should be avoided In severe cases sympathectomy gives excellent results

Conditions Associated with Hyperemia

In the second group of conditions vasospasm and venous hyperemia again are associated with exposure to cold Their

onset may have no relation to any pre-existing vascular disorders however if pre-existing vascular disease is present, the signs and symptoms produced will be more severe and destructive and will appear more rapidly with shorter exposure to less intense cold.

PERNIO

Allied to frostbite "immersion foot and trench foot pernio appears to be associated with some inherent hypersensitive vascular reaction or hypersensitivity to cold. Usually there is evidence of previous coldness of hands and feet It is known that the acra of patients with pernio maintain a lower environmental temp rature and warm more slowly than the acra of normal controls. In this there is a resemblance to acrocyanosis.

The lesions develop usually in the cool but not extremely cold weather of early fall. They appear mainly on the toes and legs, are reddish blue and slightly edematous, sometimes nodular and are characterized further by pronounced pruritus and burning especially on warming of the affected parts. In severe instances hemorrhage and bullae may be present. If there is no further exposure to cold the lesions gradually involute in 7 to 14 days, leaving postinflammatory hyperpigmentation With repeated exposures to cold, a chronic form may develop nodular lesions may recur each winter The lesions which at first may have been mild and transitory become more severe and chronic, eventually producing scarring and atrophy

The symptoms described are produced by vasospasm with an enormously dilated subpapillary venous plexus and tissue anoxia with an inflammatory reaction But they are not specific similar pathologic changes may exist with advanced Raynaud's phenomena acrocyanosis, livedo reticularis, and some types of trench and immersion foot and frostbite

Treatment demands primarily avoidance of cold even moving to a warm climate may be necessary Vasodilating agents are of aid although sympathectomy has not prevented further attacks on exposure to severe cold.

FROSTBITE

In contrast to pernio immersion foot and trench foot frost bite results from actual freezing It is not known whether the eventual damage to tissue is a result of the crystallization in freezing or of changes which take place in the blood vessels. Lewis (7) has shown that after the skin temperature of a finger placed in ice water has fallen to near 0 C there is a rhythmic rewarming up to 10 to 12 C Blaisdell (8) interpreted this as being due to changing of the spatial thermal gradient The rewarming is ushered in by erythema increased blood flow and local reflex vasodilation which result from a steep thermal gradient Later as the gradient lessens vasodilation subsides to be followed shortly by vasoconstriction With vasoconstriction a clinical pallor becomes apparent

Long exposure to cold produces a livid hue as a result of paresis in the venous side of capillaries. Intense cold stimuli are followed by a vivid red hue which is due to paresis of arterioles. The color is not caused by increased flow of blood but such paralytic arterial hyperemia can persist in the presence of increased flow when the metabolism of tissue is so far diminished that oxyhemoglobin cannot be used. This reaction represents the erythematous phase of congelation If at this phase the cold is withdrawn there is but little residuum If the cold stimulus continues, however the part becomes pallid and sequelae depend on the intensity and duration of freezing If the ultimate vasoconstriction is temporary and relaxes quickly rapid recovery is to be expected. When vasoconstriction ischemia and anoxia are prolonged thrombosis of arteries develops with subsequent tissue death necrosis, and gangrene of varying degrees Necrosis also results from actual freezing I cellular fluid with crystallization and formation f ice In addition to low air temperature contributing factors in frostbite are wetness, wind an xemia ischemia from immobility or pre existing occlusal arterial disease and lowered oxygen tension at high altitudes

Persistent paresthesia and sensitivity to cold may be expected following any type of frostbite (Fig. 5)

The best treatment is the prevention of frostbite by prophylactic measures—keeping warm and dry wearing proper boots and clothing and caring for the feet by daily washing and oiling with prevention and treatment of fissures, maceration, and tinea It has been shown by Carlson (9) that a readjustment *in the circulation adapts against cold, and that the extremities* of the adapted person tend to keep warmer allowing him to endure the cold with less discomfort and loss of efficiency The aim of definitive care is to restore natural warmth as rapidly as possible, although warmth greater than normal body temperature never should be applied. Avoidance of trauma, prevention



FIG. 5 Frostbite marked by edema discoloration and small areas of ulceration and scarring which were associated with persistent paresthesia and sensitivity to cold.

of infection, and moderate elevation of the affected extremity are essential The place of *vasodilating agents and anticoagulants* in treatment is controversial The decision to amputate should not be made hurriedly even in the presence of much necrosis and gangrene

TRENCH AND IMMERSION FOOT

Similar if not identical conditions, immersion foot and trench foot result from prolonged exposure of the feet to coldness (not freezing) and dampness. The feet are cold and numb and while they are numb pain is not prominent. Later when the boots are removed the feet are pale or cyanotic and cold and edema appears with intense pain As the feet are warmed the edema increases reflex hyperemia appears, and there is intense burning The initial phase is one of vasoconstriction and ischemia of the superficial arteries and arterioles. Orthostatic edema develops, which further interferes with circulation If exposure is prolonged lesions similar to those of pernio appear accompanied by varying degrees of anesthesia This phase is likely to persist as long as the extremity is immersed in cold water and the body exposed to chilling

The next phase is that most frequently seen by physicians and is characterized by hyperemia following removal from the wet and cold environment to a warm dry one The feet are red hot and dry—conditions similar to the clinical findings in erythromelalgia. Edema increases with hemorrhagic blebs and sometimes ecchymoses, and in more severe cases with necrosis and ulceration The anesthesia and numbness may persist for a few days, but about the eighth to tenth day after removal from the cold an intense burning develops which is similar to that of ischemic neuritis. This phase lasts about two weeks and is followed by the gradual return to normal of circulation although in severe cases gangrene may appear It should be noted that with this as with frostbite the gangrene may affect the skin only

In mild instances of trench or immersion foot the final ischemic vasospastic phase is unlikely In patients with severe cases *cold pain and stiffness persist after the hyperemic phase* has subsided There may be Raynaud's phenomena and other evidence of vasomotor instability such as hyperhidrosis These symptoms may persist for months and even years (10)

Treatment is the same as has been recommended for frostbite.

It is interesting to note that all the different clinical conditions discussed thus far are essentially vasospastic and vasoconstrictive and that the therapeutic suggestions are remarkably similar Yet there must be different anatomic and physiologic mechanisms operating to produce the different effects

Conditions Associated with Chronic Occlusive Circulatory Disorders

Still other occlusive circulatory disorders produce cutaneous symptoms that must be mentioned These are thromboangiitis obliterans (Buerger's disease) arteriosclerosis obliterans and the hypertensive ischemic leg ulcer

THROMBOANGIITIS OBLITERANS

Primarily a disease of men between 25 and 40 years of age thromboangiitis obliterans involves the medium-sized and small arteries of the extremities (usually the lower extremities) and is characterized by segmental inflammatory nonsuppurative panarteritis or panphlebitis with associated thrombosis producing organic occlusion of the vessel The capillaries are atonically dilated which accounts for the dependent rubor The clinical changes resulting are those due to ischemia The skin and nails become atrophic and later there may be spontaneous or posttraumatic ulceration and gangrene Pain is characteristic but it may be of the various types associated with intermittent claudication, ischemic neuritis, and ulceration and gangrene or it may have the form of rest pain paresthesia cold sensitivity and so on. The gangrene usually affects only one limb at a time and is acral involving the tip or the whole of a digit

As with other occlusive vascular diseases, treatment includes proper hygiene of the feet abstinence from tobacco avoidance of trauma measures effecting vasodilation and surgical procedures.

ARTERIOSCLEROSIS OBLITERANS

Another form of vascular occlusion arteriosclerosis obliterans is the result of degenerative atheromatosis involving the abdominal aorta and large and medium-sized arteries of the extremities. It is a disease of more advanced age and is found usually in men The occluding mass is an atheroma on which a throm



FIG. 6. Arteriosclerosis obliterans marked by ulceration and atrophy of skin.

bus has formed. Deposits of calcium are not infrequent The presenting symptom usually is pain of the same type as in Buerger's disease and is the result of ischemia. Physical findings ordinarily are confined to the lower extremities and consist of impaired arterial pulsations changes of color (pallor on eleva

tion, rubor on dependency and delayed filling) atrophy of the skin nails, subcutaneous tissues and muscles and ulceration and gangrene (Fig 6) Diabetes mellitus is recognized as a predisposing condition, and of course there is great current interest in the problem of impaired lipid metabolism



Fig. 7 Hypertensive ischemic leg ulcer

Treatment consists of control of the predisposing factors such as diabetes mellitus or hypercholesterolemia, increasing dilation of the arteries, relief of pain avoidance of trauma, proper hygiene of the feet and various surgical procedures.

HYPERTENSIVE ISCHEMIC LEG ULCER

Women who have and have had hypertension suffer the highest incidence of hypertensive ischemic leg ulcer the female

to male ratio being 4 to 1 The lesion is situated most frequently on the lateral surface of the ankle or lower leg It begins as a *painful erythematous plaque, turns blue and purpuric,* develops a hemorrhagic bleb and finally becomes the painful superficial ischemic ulcer (Fig 7) Such ulcers may appear spontaneously or follow minor trauma they usually are unilateral While ordinarily there is but little granulation occasionally a dense adherent sphacelus suggesting a diphtheritic ulcer is seen In



Fig. 8 Cutaneous lesions of angiokeratoma corporis diffusum.

general hypertensive ischemic leg ulcers are extremely slow t heal

Pathologic characteristics are intimal proliferati on hyaline degeneration of the media and mild periarteritis The lumen of the involved arterioles may be almost c mpletely xcluded

The treatment is that f r occlusive vascular disease in addition to measures directed t the ulcer itself Skin grafts have been performed successfully t shorten the time required f r spontane us healing

Other Cutaneous Circulatory Disorders

ANGIOKERATOMA CORPORIS DIFFUSUM

Still another condition having distinctive cutaneous lesions and associated with moderate hypertension is that rare entity known as angiokeratoma corporis diffusum (11 19) sometimes called the cardiovascular renal symptom complex. The cutaneous lesions have their onset prior to puberty and are multiple small discrete reddish purple macules and papules some of which are hyperkeratotic and of generalized distribution (Fig. 8) Histologic examination discloses large vascular spaces filled with erythrocytes and possessing a thin intact endothelial wall In the larger vessels there is vacuolation of the wall with deposition of lipid The pathogenesis of this rare syndrome is not clear

STASIC DERMATITIS AND STASIC ULCERATION

The cutaneous eruptions associated with venous insufficiency are well known to all of us in the form of stasic dermatitis and stasic ulceration. In eruptions of long standing, prominence is attained by secondary cutaneous manifestations such as pronounced lichenification secondary infection recurrent cellulitis, pachysclerosis, and others (Fig. 9) Much has been written on this subject and I shall add no more than to mention that the first object of treatment is to promote satisfactory venous return which is attempted by surgical and nonsurgical measures or by supportive bandaging It is important to realize that surgical measures frequently are contraindicated in patients with interference of deep venous circulation due to previous deep thrombophlebitis.

THROMBOPHLEBITIS

Defined as a partial or complete occlusion of a vein by a thrombus with antecedent or secondary inflammatory reaction of the wall of the vein thrombophlebitis may be divided into three clinical and etiologic groups local secondary or compli

cating and primary The local type is associated with injury of the venous wall or preexisting known disease of the wall and it can be assumed that the thrombosis is secondary In cluded in this category are those cases of thrombophlebitis due to chemical irritation mechanical injury or suppuration and thrombophlebitis occurring in varicose veins or in conjunction with ischemia of occlusive arterial disease



FIG. 9 Stasis dermatitis with ulceration, showing lichenification with excoriations surrounding ulcer

In the secondary or complicating type of thrombophlebitis it appears that thrombosis is primary and that phlebitis develops secondarily Venous stasis is thought to be the major cause since the veins of the lower extremities are involved more frequently and the patients often have been resting continually in bed. It is this type which appears in post partum and post operative patients and which complicates cases of blood dyscrasia carcinoma and heart failure

Thrombophlebitis of the primary type may appear without apparent predisposing cause and as a single episode. However, recurrent episodes of idiopathic phlebitis (thrombophlebitis migrans) are also included in this group, as is that thrombophlebitis associated with Buerger's disease.

The pathologic findings of thrombosis and inflammation of the venous wall are common to all types of thrombophlebitis, although the thrombus and the degree of phlebitis vary greatly among the several types and among cases of the same type. The thrombi may be red or white, more commonly mixed; the reaction in the venous wall may be minimal or extend well into the perivenous tissues. The primary physiologic disturbance is obstruction of venous flow and depends on the size of the thrombus as well as the site and size of the involved vessel. Clinical cutaneous manifestations vary also with the site of the inflammatory reaction.

In acute superficial thrombophlebitis, linear inflammatory erythema outlines portions of the course of the vein with local tenderness and pain. Edema is not prominent. In deep thrombophlebitis the limb is edematous, the skin may be cyanotic and exhibit prominent superficial veins. The latter may be more readily visualized with infrared technics.

With recent greater appreciation of the influence of venous stasis as an etiologic factor in secondary thrombophlebitis, the incidence of this disorder has been greatly decreased. Early ambulation post partum and postoperatively, exercises and adequate hydration are most important.

Anticoagulants are given both for prevention and for treatment. Local treatment consists of elevating the affected extremity and applying heat to it until signs of inflammation have subsided. Moderate exercise in bed is permitted after the third day from onset of symptoms. Supportive bandaging usually is not necessary with superficial thrombophlebitis, but should be used in deep thrombophlebitis as soon as the patient's legs become dependent. With proper support, chronic deep venous insufficiency *may be prevented in many instances.*

ROSACEA

The commonly seen rosacea may also be considered, in part at least, a circulatory cutaneous disorder It occurs in those individuals with an especially labile vasomotor reaction who are likely to respond to all sorts of stimuli with vasodilation. At first there may be psychogenic blushing which is pure nervous cholinergic vasodilation with increased arteriolar flow This is seen frequently in physicians offices while a woman is



FIG 10 Rosacea with rhinophyma.

undressing as a blotchy erythema over the face upper back shoulders and chest It fades quickly but to the inexperienced eye may briefly simulate an eruption or exanthem As various stimuli—psychogenic and other—add their respective amounts of vasodilation the previous transient flushing becomes more lasting the final result being a permanent erythema with telangiectasia and increased oiliness of the skin (Fig 10) The seborrheic hyperactivity may exist at the outset or appear later as a result of the chronic hyperemic state Treatment is directed in two channels first, the avoidance of those stimuli that pro-

duce vasomotor flushing and second, measures directed toward lessening of sebaceous hyperactivity

Opportunities for Investigation

With all that has been said heretofore concerning many apparently unrelated disorders of cutaneous circulation a vast realm of physiology is yet to be explored. Actually as was indicated in the introduction to this paper all but a few dermatologic disorders are associated with some disturbance of cutaneous circulation An instance is the arterial hyperemia of an inflammatory reaction. Vivid redness may result from acute sunburn and dusky shades of red and blue may be effects of the chronicity of the eruption the depth of the pathology the amount of infiltrate the thickness of the squamous cell layer and so on and from simple lichenification psoriasis, and lichen planus.

I should like to point out some interesting problems wherein our knowledge of basic physiology is lacking, hoping that some may be stimulated toward greater investigation thereby

The fascinating cutaneous vascular physiology of the atopic individual is one of these problems Characteristic are the white dermographism seen more frequently in patients with atopic dermatitis than in other dermatoses the delayed blanching of Lobitz and Campbell and a tendency toward decreased vasoconstriction in the antecubital and popliteal fossae and increased vasoconstriction of toes and fingers in a cold room together with delayed vasodilation of toes and fingers and increased vasodilation of the antecubital and popliteal fossae in a hot room (15)

The influence of estrogens is a dermatologic problem in its relationship to symmetrical erythema of the palms and soles and the small spiders that develop during pregnancy Furthermore why are so many patients with vasoconstrictive disorders women? The association of liver disease with pulsating spiders and the development of the ruby spot as we grow older are further examples

We still do not know much concerning the control of circulation by the central nervous system and the reflexes, and we know next to nothing of other factors enhancing vasoconstric tive phenomena, such as the increase which the presence of cryoglobulinemia and cold agglutinins produces in the suscepti bility to frostbite and Raynaud's phenomena. The mechanism of sludging is interesting in these and in other disorders.

The contemplation of chemicals having influence on physiologic circulatory mechanisms is overwhelming for it involves the entire realm of autonomic stimulants and blockers—those that act centrally peripherally or locally and those that are humoral The intriguing development of knowledge concerning the syndrome of the functioning carcinoid is but an unusual case in point here 5 hydroxytryptamine (serotonin) liberated by cells of the functioning tumor produces a series of symptoms which is manifested especially by frequent profuse diarrhea recurrent asthmalike attacks lesions of the valves of the right side of the heart, and—more important in this discussion—episodic intense flushing of the skin as an indication of a circulatory cutaneous reaction

Numerous questions naturally arise in this speculation For instance what is the role of the mast cell with its load of serotonin histamine and heparin (all potent chemicals involving circulation)? However I must leave to others the attempt to elucidate these far reaching problems which involve not only dermatology but all of medicine

If there must be a summary to this paper it is simply this A wide range of circulatory cutaneous problems have been discussed but more importantly the deficiency of current knowledge of the underlying physiologic mechanisms has been stressed.

REFERENCES

1 Ormsby O S. and Montgomery Hamilton *Diseases of the Skin* 8th Edition Lea & Febiger Philadelphia Pa., 1954

2. Pillsbury D M Shelley W B., and Kligman A M *Dermatol gy* W B Saunders Company Philadelphia Pa 1956.
3 Rothman Stephen. *Physiology and Biochemistry of the Skin* The Univerity of Chicago Press, Chicago Ill., 1954
4 Allen, E V Barker N W and Hines, E A Jr *Peripheral Vascular Diseases* 2nd Edition W B. Saunders Company Philadelphia Pa., 1955
5 Wolstenholme, G E W and Freeman J S Ciba Foundation Symposium *Peripheral Circulation in Man* Little, Brown and Company Boston, Mass., 1954
6. Feldaker Mauri Hines, E A., Jr and Kierland, R. R. *Livedo reticularis with ulcerations. Circulation* *13* 196-216 (1956)
7 Lewis, T Observations upon the reactions of the vessels of the human skin to cold. *Heart* *15* 177 208 (1929-1931)
8 Blaisdell, R. K. Quoted by Stephen Rothman, reference 3
9 Carlson, L D Changes in peripheral circulation with exposure to cold, in G E W Wolstenholme and J S Freeman, Ciba Foundat on Symposium. *Peripl eral C culation in Man* Little, Brown and Company Boston, Mass., 1954 Pages 92 101
10. Shafer J C., and Thompson A W Local cold injury A report of sequelae. *Am Med Assoc Arch Derm tol* *72* 335-317 (1955)
11 P ttelkow R. B Kierland, R. R. and Montgomery Hamilton. Angiokeratoma corporis diffusum *Am Med Assoc Arch. Dermatol.* *72* 556-561 (1955).
12 P ttelkow R B Kierland R. R. and Montgomery Hamilton. Polariscopic and histochem cal studies in angiokeratoma cor poris diffusum *Am Med Assoc Arch Dermat l* *76* 59-64 (1957).
13. Baer R. L. The development of the concept of atopic dermatitis. *Am Practit oner and Dig Treatment* *6* 1075-1078 (1956)

Discussion

Dr. J Benison (*Ford Hospital Det oit Micl*). I would like to ask the panel and other members present about data on sk n graft ng and regeneration from epidermal appendages.

Dr. Kierland R. A. Good and lso Haxthausen f Denmark have done a great deal of work with grafted skin in tudies on immunol ogy Dr Curtis and his group at Ann Arbor ha done some work with skin grafting of cond tions in wh h there has been a deficit of

cutaneous circulation such as in necrobiosis with ulceration, and so on In our own experience, if the deficit goes down to the muscularis, there are no skin appendages left If we feel there are skin appendages present, we allow epithelization to take place spontaneously rather than resorting to grafting unless the deficit is so large in circumference that we think the patient will be saved time and money ultimately because of the rapidity of healing of a good graft. It is well known that epidermal regeneration following dermabrasion originates from the remaining portion of the dermal appendages.

STATEMENT FROM THE AUDIENCE Dr Converse at New York University has been doing work in this area. He is heading a New York Academy of Science Symposium on skin grafting

DR. ROTHMAN *Physiological Reviews* will soon bring out an excellent review by Dr Sherwood Lawrence from New York University on transplantation and grafting discussing both immunological and practical aspects.

III Sebaceous Gland Secretion

SIGNIFICANCE OF CHANGES IN PILOSEBACEOUS UNITS IN ACNE AND OTHER DISEASES

EUGENE J VAN SCOTT

Dermatology Service, General Medicine Branch National Cancer Institute Bethesda Maryland

The lesion of acne generally has been considered to result from the comedo a keratinous mass occluding the follicular orifice (1,2) Recent evidence indicates that hyperkeratinization of the duct of the sebaceous gland occurs prior to the occlusion of the follicular lumen and that the acne lesion appears to be initiated at that time (3) Thus acne is one of few cutaneous diseases in which the sebaceous gland appears to be the site of the primary lesion.

Whether the changes occurring in the sebaceous gland and follicle in acne are peculiar to this disease is unknown The aim of this paper is to review the changes that take place in the pilosebaceous unit during the course of the lesion of acne and to evaluate the specificity of these changes by comparing them to somewhat similar changes that may be found in pilosebaceous units involved in other diseases.

The description of the lesion of acne in this paper is based on studies of serially cut histological preparations of skin from patients and reconstructed models of pilosebaceous structures. The patients, the techniques, and observations have been described in an earlier publication (3) The same techniques have been applied to the study of pilosebaceous units involved with diseases other than acne

Normal Pilosebaceous Units

The sebaceous gland is derived from the epithelium of the follicular neck and anatomically is inseparable from the hair

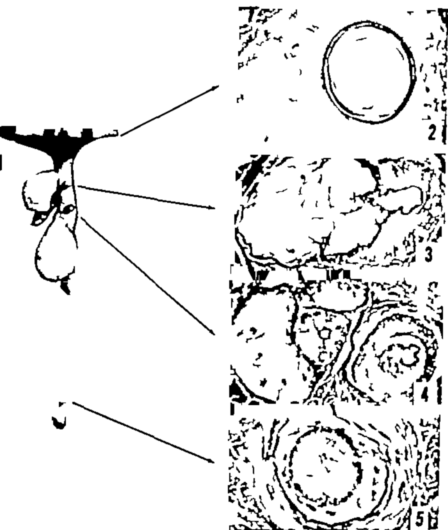


PLATE I

follicle. Its structure and function therefore would seem to be best dealt with in light of the entire pilosebaceous unit. This discussion deals primarily with the pilosebaceous units from the upper back and bearded skin of the face.

PILOSEBACEOUS UNITS OF THE UPPER BACK (PLATE I)

The majority of pilosebaceous units of the upper back of young adult men and women were found to possess two hair root portions which project downward from a common follicular neck (5) The hairs produced by both hair roots travel through the lumen of the follicular neck and emerge at the surface through a common follicular orifice. The growth cycle of each hair root is independent of the other although both may be found simultaneously in the same stage of the cycle

Each hair root possesses its own sebaceous gland attached to the follicle at the junction of the root and the follicular neck. The size of sebaceous glands is quite variable and may be several fold larger than that of the glands shown in Fig 1 The

PLATE I Balsa wood model and photomicrographs of normal pilosebaceous unit of upper back of 24-year-old white man. Arrows indicate levels of pilosebaceous unit from which photomicrographs were taken (From material cited by W Montagna and E. J Van Scott in *B ol gy of Hair Growtl* Academic Press, New York, 1958.)

Fig 1 Model of pilosebaceous unit. Pilosebaceous unit possesses two hair roots attached to a common follicular neck. Each hair root has its own sebaceous gland (white). Upper hair root is in telogen (resting) phase of the growth cycle lower hair root is in anagen (growing) phase of the growth cycle.

Fig 2 Photomicrograph of transverse section through upper follicular neck. Strat m corneum loosely surrounds hair hafts in concentric rings. ×10

Fig 3 Phot microgra h of section through duct of upper sebaceous gland shown on model Small amount of keratinous material is present in duct. Three hair in follicular lumen s nce pilosebaceous unit here possesses only two hair roots, one ha r must represent a telogen ha r rema ng from an earlier growth cycle. ×75

Fig 4 Sebaceous gland duct, of lower sebaceous gland shown on model, seen on right side of photomicrograph. Root of telogen hair in center of photograph. ×75

Fig 5 Hair root in anagen phase of the growth cy le. ×125

duct of the sebaceous glands empties directly into the lumen of the follicular neck thus a single lumen provides passageway for both the hairs and the products of the sebaceous gland. Normally a small amount of keratinous material is present in the lumen of the duct (Figs. 3 4)

PILOSEBACEOUS UNITS OF THE MALE BEARD REGION

Most of the pilosebaceous units of the skin of the male beard possesses a single hair root in distinction to the twin hair roots of pilosebaceous units of the upper back The lumen of the follicular neck of the beard is divided into *two* discrete channels that are isolated from one another by a wall of keratinous material The hair passes through one channel while the other channel serves as a conduit for connection between the duct of the sebaceous gland and the surface of the skin

Changes in Pilosebaceous Units In Acne

EARLY CHANGES OF ACNE (PLATE II)

The first recognizable change of acne in a pilosebaceous unit is hyperkeratinization of the duct of the sebaceous gland. In the skin of the upper back this change becomes manifest in the pilosebaceous unit at a time when its hair roots are in the telogen (resting) phase of the growth cycle The keratinous material produced by the sebaceous duct appears in the follicular neck as a peripilar sheath An infiltrate of leukocytes within the corium surrounds the pilosebaceous unit at this time and is maximally dense at the level of the sebaceous duct Leukocytes invade the follicular lumen at the level of the sebaceous duct accumulating first as intraluminal microabscesses (Fig 9) and later fill the entire lumen of the follicular neck The accumulated mass of leukocytes (pus) appears to compress the keratinous material within the follicular neck into an impacted plug that occludes the follicular lumen at its epidermal orifice The follicular neck becomes elongated and distended until it ruptures either onto the skin surface above or through the sides of the follicular neck

The primary origin of the lesion of acne within the duct of the sebaceous gland is perhaps more clearly demonstrated in pilosebaceous units of the male beard skin In these units where the lumen of the follicular neck is divided into two separate channels the changes that follow the initial hyperkeratinization of the sebaceous duct are confined solely to the sebaceous excretory channel within the follicular neck, whereas no discernible changes occur within the channel through which the hair passes (Figs. 10–12)

LATER CHANGES OF ACNE

A severe inflammatory reaction around the follicular neck is associated with rupture of the walls of the follicular neck by the pus contained in its lumen The entire follicular neck may thus be destroyed In this event the lower portion of the pilosebaceous unit is isolated within the corium having no connection with the epidermal surface. Later it may be obliterated by a granulomatous type reaction. Such obliterated units can be identified by the presence of nests of foreign body giant cells, hair shafts, epithelial tissue remnants, keratinous debris and amorphous material.

The remaining upper follicular neck of the disrupted pilosebaceous unit persists as a blind sac. Since neither sebum nor hair pass through its lumen the keratinous material produced by its walls accumulates and forms a comedo Such comedones are thus sequelae of a destructive lesion of acne and are quite different in nature from the keratinous mass occluding the follicular neck in the early lesion

Evaluation of Changes in Pilosebaceous Units in Acne

SIZE OF SEBACEOUS GLANDS

Although the impression may be gained from histological preparations that sebaceous glands in acne tend to be larger than those of normal skin the actual size of the glands has not been measured. Pilosebaceous units of normal skin have both large and small sebaceous glands. Furthermore the presence





PLATE III

quent course of the latter lesion however is quite different from that found in acne Occlusion of the follicular orifice with keratinous material occurs, but leukocytes do not invade the follicular lumen. The follicular neck becomes markedly distended with sebaceous material forming a noninflammatory cyst (Fig 14)

Occlusion of the follicular lumen occurs in a number of other diseases without subsequent development of acne or acneiform lesions. Such is the case for example in both ichthyosis and psoriasis in which the follicular lumen may be completely occluded with densely packed keratinous material (Fig 15).

Discussion

Neither keratinization of the duct of the sebaceous gland nor occlusion of the entire lumen of the follicular neck are changes specific for the lesion of acne. The specific feature of the lesion would seem to be the concomitant invasion of the follicular lumen by leukocytes and the subsequent courses of the lesion resulting therefrom.

The early migration of leukocytes into the follicular lumen at the level of the sebaceous duct in acne suggests the presence of a chemotactic substance within the duct. Whether sebum of patients with acne is qualitatively different from sebum of normal individuals is unknown Washburn and Liese (5) found no difference in the cholesterol content of sebaceous material from the forearm in the two groups. The iodine number of the sebaceous material was slightly increased in the patients with acne but the authors questioned the significance of this increase

PLATE III Pilosebaceous units in lesions other than acne.

Fig 13 Early lesion of steatocystoma multiplex showing keratinization of sebaceous gland duct. From the anterior chest of a 26-year-old Negro man. ×50

Fig. 14 Cyst of steatocystoma multiplex, resulting from occlusion of the follicular neck. Lesion is noninflammatory ×40

Fig 15 From lesion of psoriasis. Follicular neck occluded with dense mass of keratinous material. ×50.

Summary

The first recognizable change in pilosebaceous units involved with a lesion of acne consists of *hyperkeratinization of the duct* of the sebaceous gland. Leukocytes invade the follicular lumen at the level of the sebaceous duct and later fill the entire lumen of the follicular neck. The accumulated mass of leukocytes appears to compress the keratinous *material within the follicular* neck into an impacted plug that occludes the follicular lumen at its epidermal orifice. Rupture of the wall of the follicular neck results in destruction of the mid follicular neck, isolating the lower portion of the pilosebaceous unit from the remaining upper follicular neck. The lower portion eventually may be obliterated by a granulomatous type reaction while the upper follicular neck persists as a blind sac that produces a comedo.

Hyperkeratinization of the duct of the sebaceous gland and occlusion of the follicular lumen with keratinous material are not specific for acne since they occur in other diseases. Invasion of the sebaceous gland duct and follicular lumen by leukocytes histologically differentiates the early lesion of acne from other lesions involving the pilosebaceous unit.

REFERENCES

1 Unna, P. G. *The Histopathology of the Diseases of the Sk[in]*. Translated by N. Walker, Clay Co., Edinburgh, 1896.
2 Lynch, F. W. *Arch. Dermat. and Syphilol.* 4: 593 (1910).
3 Van Scott, E. J. and MacCardle, R. C. *J. Invest. Dermat.* [illegible]: 105 (1956).
4 Prose, P. H., Baer, R. L. and Herrmann, F. *J. Invest. Derm.* [illegible]: 123 (1953).
Washburn, S. L. and Liese, C. J. *J. Lab. Clin. Med.* 41: 1[illegible] (1953).

Discussion

Dr. R[illegible]: It will be interesting to speculate on possible specific causes for the special development of acne lesion. After Dr. Van Scott has shown so dramatically that there is plugging of follicles in other conditions where no acne will develop

DR. SULZBERGER. Of course I think the very careful reconstructions that Dr Van Scott has made and that were shown so beautifully bring in certain new points. I think the principal new point, which was the newest to me, was that this keratinization does not come from the surface downwards, but starts further down at the orifice of the sebaceous duct and then moves upward in the follicle. I don t know how much difference that makes in principle regarding the genesis of acne because the old concept and Dr Van Scott s concept agree that the thing that occurs then regardless of the exact point of origin of this keratin, is an obstruction of the orifice. I cannot quite agree with Dr Van Scott that there isn t a direct relationship between the size of the sebaceous glands and the amount of sebum excreted, because there is good work that seems to point to the opposite. There is a direct correlation between the size of the sebaceous gland elements and the amount of sebum they produce and deliver to the surface. I am referring particularly to the work of Miescher and his group. I would like to hear Dr Van Scott s comments on that.

One thing that I missed in his presentation is that the quality of the sebum and the chemical properties of all material that is in the occluded pilosebaceous apparatus may have something to do with the leukotaxis and the production of the acne lesion It is quite possible that, under the hormonal stimuli the conditions of adolescence and the state of the pilosebaceous apparatus in response to new hormonal stimuli, the composition of sebum may be different chemically from the sebum in steatocystoma multiplex which he showed here and which didn t produce the inflammation which accompanies the acne lesion. I think the best hypothesis would be that in steatocystoma multiplex something from the pilosebaceous apparatus gets into the corium which is different from that which comes out in acne. And in the latter case, the material that comes out is inflammation-provoking Included in that, of course, are bacteria which may be trapped in part of the occluded follicle, other microorganisms, products of these living agents, and also materials that are being excreted with the sebum that may come from internal sources such as ingested food.

I am quite sure that in the case of bromide and iodide eruption the best hypothesis is that these materials are actually excreted with the sebum into the pilosebaceous orifice and if that is plugged more of the irritating material gets into the cutis. Probably in the case of some foods that hypothesis might also apply for instance in those cases in which acnes are definitely made worse and new showers of lesions are brought on by the ingestion of such things as chocolate and shell fish. Also there is the possibility that products of distant foci of infection may somehow get into these follicles via the blood stream and be excreted into the openings or around the plugged

follicles. So all those conditions might account for the final difference between the noninflammatory occlusion as is seen in cysts of steatocystoma multiplex and the final inflammatory lesion of acne vulgaris. In that connection I think I should point out that as all of you know there are many lesions in acne vulgaris that are noninflammatory too. There are many comedones that show practically no, at least no gross, clinical inflammation around them and many small cystic lesions, milia-like lesions, and even fairly large cysts that from all clinical points of view have practically no inflammation and resemble those in that respect, at least clinically, grossly, macroscopically, the lesions of steatocystoma multiplex.

DR. VAN SCOTT: I feel that those lesions which do not have inflammatory reactions could very well be the result of previous lesions of acne. In this late lesion the comedo is the accumulated keratinous material in the follicular neck that remains isolated after the destruction of the lower portion of the pilosebaceous unit.

I do agree with you in regard to possible qualitative differences in sebum that might explain the occurrence of different lesions. The reason I said that sebaceous gland size may not necessarily correlate with function is to explain possibly those lesions of acne which occur in pilosebaceous units with small sebaceous glands. These lesions may be related to how much sebum is secreted by the gland rather than the size of the gland. Certainly acne does occur in the areas on the skin where the sebaceous glands are largest and where the sebaceous output is greatest.

DR. ROTHMAN: I think, as Dr. Sulzberger pointed out, that it is an untenable view that the amount of sebum produced does not depend directly on sebaceous gland volume. I think this has been proved many times with strict quantization, and I don't see any evidence to the contrary. If you agree, and I think you brought it out very beautifully, that there might be in the sebum some product which is responsible for leukotaxis and inflammatory reactions and you agree that the concentration of this product may be independent of glandular volume, you may of course get acne lesions in pilosebaceous units which have small sebaceous glands. That has nothing to do with the well-established fact that the greater the gland volume the greater is the sebum production. I think that is very well proved in many respects, and particularly through the work of Miescher. Wouldn't you agree with that?

DR. VAN SCOTT: Yes. I just wonder about the exception. The correlation does exist generally that the size of a sebaceous gland corresponds to the amount of sebum excreted. This is true of whole populations of glands. Now whether this always is true when individual units are compared to one another I do not know, whether

there are large sebaceous glands which secrete little sebum and small sebaceous glands which secrete large amounts.

DR. ROTHMAN It is very hard to fathom how sebum can be produced in large amounts, if there is no mitotic activity in the basal layer of the sebaceous gland. This activity will be the only decisive factor on how many cells are being formed and indirectly how many cells will be destroyed I do not think there are exceptions to that. There might be a large sebaceous gland which does not function, which does not fall apart. This is true for sebaceous adenomas and if that is what you are talking about, we agree.

DR. VAN SCOTT Yes, the size of the sebaceous gland could either reflect degree of activity or it may simply be large because it retains its product.

DR. SUSKIND I would like to point out that there is available a fairly good tool by which we can follow the evolution of an acne type of process, which from the point of view of the morphology of the lesi ns and the clinical evolution of the lesions is very similar to that of acne vulgaris. I refer to the acne which one can induce by the application of chlorinated naphthalenes and chlorinated diphenyls on the skin. One can trace the evolution from the earliest possible changes that one can see to full blown lesions all of which are also seen in acne vulgaris. There may be certain metabolic dissimilarities which I am not prepared to discuss. But I think one can note in induced acne that the first thing that seems to occur is a hyper keratinization either at the sebaceous duct orifice or as in the case of occupational acne or induced acne, at the infundibulum, that is, the opening of the follicle. An obvious occlusion of either the duct or follicle follows this early keratinization. Subsequent to this we see (this may be where acne vulgaris differs from induced acne) inflammatory changes early or may see inflammatory changes after large cystic lesions are developed. But one very interesting similarity is that under this stimulation the sebaceous glands seem to break down. What really happen is that most undifferentiated sebaceous gland cells at the bottom of the acini do not form the lipid-bearing cells. They form undifferentiated epidermal cells which are indistinguishable from ordinary follicular cells. So instead of having sebaceous gl nds, we ha e a thick follicular epithelium which actu ally replaces the sebaceous glands This is not true atrophy This is imply replacement by undifferentiated cells. This occurs also in cne lg ris. One can demonstrate within the follicle the formation of small micropustules which apparently are not d e to bacteria. They re due to the chemical material which has been applied. In the case of nduced acne or in the case of acne vulgar s, a chemical stimulation occurs loc lly and it must be a metabolic product which

I think one can speculate is similar to that of the chlorinated naphthalenes and chlorinated diphenyls. This is something which one should bear in mind when one thinks of the possible local chemical stimulation which gives rise to the similar changes in acne vulgaris and in induced acne. They are very similar—almost identical.

DR. ROTHMAN: I do not believe that Dr. Lorincz will speculate on that in his presentation. I call on him to see what he has to say about this material which is leukotactic and inflammatory.

DR. LORINCZ: This is pure speculation. One might possibly think of a breakdown product of a sterol or some steroid hormone. If one strips two of the rings, four and five, from the phenanthracene nucleus of steroids, one obtains naphthalenic compounds with substituted groups that in a rough way resemble the chlorinated naphthalenes and other acnegenic agents. It seems fairly plausible that bacteria, the normal flora that reside in the follicle, may do this metabolic trick and so give rise to acnegens. Observations that might correlate with this view are the well known examples of steroid acne. Administration of corticosteroids will produce acne which may lack the sebaceous gland component, but the other basic part of the lesion, the abnormal follicular keratinization, is present. There has also been some fairly recent Russian work which claims to show that the amount of androgenic steroid in sebum in acne is actually increased.

DR. PINKUS: In seeing these people who work in the Halowax (chlorinated naphthalene) manufacture, it is surprising that even with severe degrees of acne on the face and neck and possibly even the shoulders I do not think I have ever seen one who had the same lesions on the scalp. One of our ambitious instructors at Wayne University thought he would use some of this chlorinated compound, Halowax, in microsporum audouini infections of the scalp to see if he could obliterate the hair follicle temporarily. So he applied it very carefully to lesions on the scalp and several children developed *severe chlor-acne of the face but absolutely no reaction of the scalp.* This would fit in with Dr. Van Scott's statement that there is something different about these follicles on the scalp.

DR. SUSKIND: I want to point out that there are clinical variations in these problems that one has to consider. In a series of 930 cases of occupational acne of varying severity which I followed in one industrial plant, there were at least a half dozen severe cases in which nearly every follicular orifice was affected, including the scalp. One has to assume that there are differences perhaps in individual responsiveness, perhaps differences in the degree of chemical stimulation and of the susceptibility or degree of exposure. If great enough, *acne lesions may even be found in the scalp.*

BIOCHEMICAL AND HORMONAL ASPECTS OF SEBACEOUS SECRETION*

ALLAN L. LORINCZ

Section of Dermatology Department of Medicine, University of Chicago Chicago Illinois

In mammals including man the skin surface is covered by a film composed of an emulsion of fatty and aqueous materials which also permeates the stratum disjunctum of the horny layer This film has significant protective and other biological functions. It helps maintain the normal hydration and pliability of the horny layer delays or regulates the absorption of many foreign substances, and contributes to protection against exogenous infections and infestations. It partly carries the precursor of vitamin D and contains odorous substances involved in animals in the recognition of their own and foreign species and in sexual attraction. Other yet unrecognized functions in all probability remain to be uncovered.

The lipid components of this surface film derive mainly from sebum, the excretory product of sebaceous glands. Other lipids released from keratinizing epidermal cells and in certain areas from apocrine sweat secretion also contribute to the surface lipid film

Phylogenetically the first true ancestors of mammalian sebaceous glands occur in reptiles (1) In these reptilian glands the inside of each cell undergoes fatty decomposition while the periphery keratinizes (2) This linkage of fatty decomposition

* Based largely on material assembled for article prepared jointly with R. B. Stoughton for *Physiological Reviews* entitled, "Specific Metabolic Processes of the Skin.

I think one can speculate is similar to that of the chlorinated naphthalenes and chlorinated diphenyls. This is something which one should bear in mind when one thinks of the possible local chemical stimulation which gives rise to the similar changes in acne vulgaris and in induced acne. They are very similar—almost identical

DR. ROTHMAN I do not believe that Dr Lorincz will speculate on that in his presentation I call on him to see what he has to say about this material which is leukotactic and inflammatory

DR. LORINCZ This is pure speculation One might possibly think of a breakdown product of a sterol or some steroid hormone. If one strips two of the rings, four and five from the phenanthracene nucleus of steroids, one obtains naphthalenic compounds with substituted groups that in a rough way resemble the chlorinated naphthalenes and other acnegenic agents. It seems fairly plausible that bacteria the normal flora that reside in the follicle, may do this metabolic trick and so give rise to acnegens. Observations that might correlate with this view are the well-known examples of steroid acne Administration of corticosteroids will produce acne which may lack the sebaceous gl nd component but the other basic part of the lesion the abnormal follicular keratinization is present. There has also been some fa rly recent Russian work whi h cl ims to show that the amount of ndrogen steroid in sebu n acne is actually increased.

DR. PINKUS In seeing these people who work in the Halowax (chlorinated naphthalene) manufacture, it is surprising that even with severe degrees of acne on the face and neck and possibly even the shoulders I do not think I have ever seen one who had the same lesions on the scalp One of our ambitious instructors at Wayne Uni ersity thought he would use some of this hlor nated compound Halowax in microsporum audouini infect ons of the scalp to see if he could obliterate the l ir follicle temporarily So he applied it very carefully to lesions on the scalp and several children developed severe chlor-acne of the f ce but absolutely no reaction of the scalj This would fit in w th Dr Van Scott s statement that there is something different abo t these follicles on the scalp

DR. SUSKIND I want to point out that there are linical v riations in these problem that one has to con ider In a series of 230 cases of oc upational acne of rying severity which I foll wed in one industrial lant there were at least a l lf dozen severe cases in which nearly every f lli ular orifi e was affected including the scalp. One has t aw e that th r are differences perhaps in individual re spon s enes perh ps differences in the degree of chemical timu lation nd f the suscep til ility or degree of exp sure is gr at enough, acne lesions may even be found in the scalp

glycerides of palmitic, stearic and oleic acids with only small amounts of other lipids, whereas the surface fats in man contain about 30 per cent of unsaponifiable material and the fatty acids are present to the extent of about 60 to 65 per cent. These fatty acids occur in much richer variety and are esterified not only with glycerol but also with sterols and wax alcohols. Also in contrast to depot fat which has essentially the same composition in all mammalian species, many striking species differences exist in the surface lipids of various mammals.

During the past decade intensive work has been done especially in man in elucidating the chemical constituents of sebum hair fat, or the surface lipid film. These studies opened new chapters in lipid biochemistry abolished the concept that only fatty acids with even numbers of carbon atoms occur in natural lipids, and stimulated work that uncovered the intermediary metabolism of cholesterol synthesis. The names of Rothman Weitkamp Nicolaides, and their co-workers and of MacKenna, Wheatley and associates have been especially prominent in this analytical work. Reviews on the chemistry and biochemistry of surface lipids or sebum have been compiled recently by Rothman (5) and by Wheatley (6–8)

Fatty acids on the skin surface occur in the free state as well as esterified with glycerol wax alcohols, and sterols. Monoglycerides and diglycerides as well as triglycerides occur (9) The relative percentage of free fatty acids is variable This variability is no doubt caused by progressive lipolysis which occurs on the skin surface or during storage of hair fat (10) largely as a result of lipolytic enzyme activity Microorganisms on the skin surface possess such lipolytic activity and there is good histochemical evidence for the presence of lipases in sebaceous gland ducts (11–13) Nicolaides and associates furthermore have shown lipolysis of radiocarbon-labeled tripalmitin to occur when applied to the skin surface. Very recent studies suggest that possibly all the fatty acids in freshly formed sebum may be in esterified form (13)

The first detailed study of the fatty acids in human hair fat was carried out by Weitkamp Smiljanic and Rothman by

and keratinization is also seen in mammals in the formation of vernix caseosa and smegma from surface epithelium and further in the lipid rich contents of keratin cysts. It is possible to speculate that all epidermal cells have the potentiality not only of keratinizing but also of undergoing fatty decomposition. Surface epidermal cells normally differentiate to form primarily keratin whereas sebaceous cells differentiate to form sebum. Under some circumstances however, such as the partial occlusion of the sebaceous gland duct, the germinative epithelium of sebaceous glands can give rise to epidermal cells which will keratinize and vice versa, under some circumstances of irritation sebaceous transformation can occur in cells normally destined to produce keratin (3).

Morphologically, sebaceous glands are generally appendages of the outer root sheath of hair follicles and open to the skin surface via the pilosebaceous canal. They usually have a multiple acinar structure and produce sebum by a holocrine mechanism. The outermost layer of cells is the germinative epithelium of the gland. Mitotic activity in this layer as well as in the epithelium of the sebaceous ducts gives rise to the continuous stream of sebaceous cells that move from the periphery to the center of the gland. As the cells move in this stream they grow progressively larger as the result of intracytoplasmic accumulation of numerous droplets of fat which remain separated by a protoplasmic meshwork in contrast to the single large fat droplet seen in body depot fat cells. Finally, in the center of the gland the sebaceous cells become so distended with fat that their cell walls disintegrate liberating the enclosed lipid. Other cell constituents which have undergone disintegration in the process are also released. Histologic observations indicate that most of the lipid which accumulates in sebaceous cells does not arise by reorganization of cytoplasmic constituents of the cell but rather by accumulation of precursor materials from the outside. This lipid apparently accumulates initially in the Golgi elements (4).

Chemically, there are vast differences between skin surface lipids and body depot fat. The latter consists mainly of tri

glycerides of palmitic, stearic, and oleic acids with only small amounts of other lipids, whereas the surface fats in man contain about 30 per cent of unsaponifiable material and the fatty acids are present to the extent of about 60 to 65 per cent. These fatty acids occur in much richer variety and are esterified not only with glycerol but also with sterols and wax alcohols. Also in contrast to depot fat which has essentially the same composition in all mammalian species, many striking species differences exist in the surface lipids of various mammals.

During the past decade intensive work has been done especially in man in elucidating the chemical constituents of sebum, hair fat or the surface lipid film. These studies opened new chapters in lipid biochemistry, abolished the concept that only fatty acids with even numbers of carbon atoms occur in natural lipids, and stimulated work that uncovered the intermediary metabolism of cholesterol synthesis. The names of Rothman, Weitkamp, Nicolaides, and their co-workers and of MacKenna, Wheatley and associates have been especially prominent in this analytical work. Reviews on the chemistry and biochemistry of surface lipids or sebum have been compiled recently by Rothman (5) and by Wheatley (6–8).

Fatty acids on the skin surface occur in the free state as well as esterified with glycerol, wax alcohols, and sterols. Monoglycerides and diglycerides as well as triglycerides occur (9). The relative percentage of free fatty acids is variable. This variability is no doubt caused by progressive lipolysis which occurs on the skin surface or during storage of hair fat (10), largely as a result of lipolytic enzyme activity. Microorganisms on the skin surface possess such lipolytic activity, and there is good histochemical evidence for the presence of lipases in sebaceous gland ducts (11–13). Nicolaides and associates, further more, have shown lipolysis of radiocarbon labeled tripalmitin to occur when applied to the skin surface. Very recent studies suggest that possibly all the fatty acids in freshly formed sebum may be in esterified form (13).

The first detailed study of the fatty acids in human hair fat was carried out by Weitkamp, Smiljanic, and Rothman by

amplified distillation of their methyl esters (14) A homologous series of normal straight-chain acids was found with all members from C_7 to C_{22} (except C_1 and C_{21}) being present (Table I).

TABLE I Appro imate compositio of the methyl esters of free fatty acids in human hair fat (14)

Carbon toms	Per cent present	Per cent unsaturated
7	0 07	0
8	0.15	0
9	0 20	0
10	0.33	0
11	0 15	T ace
1	3 5	1 (– H)
13	1 4	3 (– H)
14	9.5	15 (– H)
15	6.0	25 (– 2H)
16	36 0	50 (– H)
17	6 0	67 (– H)
18	23 0	80 (– 4H)
20	6.5	85 (– 2 5H)
22	2 0	–
Bottoms	4 0	–

Fatty acids with even numbers of carbon atoms were present in much larger amounts than those with odd numbers of such atoms. Unsaturated acids were also found which differed from those present in commonly occurring fats. In the unsaturated compounds most of the double bonds were between the ninth and tenth carbon atoms from the carbon which is farthest from the carboxylic end On splitting at such double bonds one fragment of 9 carbon atoms is always present Recently James and Wheatley (15) have confirmed all these findings by analyzing surface lipid from the human forearm by means f gas-liquid chromatography In addition these workers found very small amounts of single-branched and multiple branched acids throughout the series which could not have been detected by the previous amplified distillation technique The free fatty acids on the skin surface have important antibiotic properties. The long chain unsaturated acids particularly suppress some kinds of

bacterial growth (16,17) whereas the shorter-chain saturated compounds are antifungal. Rothman and associates (18) have presented good evidence that the spontaneous cure of epidemic ringworm of the scalp at puberty is related to the increased sebaceous gland activity at that time. The extent of spreading of a film of surface lipid as a monomolecular layer on water (19,20) appears to be determined almost entirely by the amount of free fatty acids that are present. Such spreading on water surfaces, therefore, as pointed out recently by Herrmann and asso-

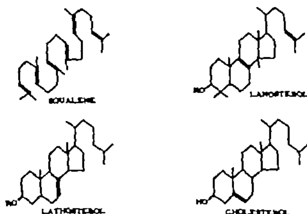


FIG. 1. Structural formulas of squalene, lanosterol, lathosterol, and cholesterol.

ciates (21), cannot be used as a measure of the amount of surface lipid or sebum being produced.

Squalene is the principal hydrocarbon present in human surface lipid and it accounts for about six to eleven per cent of the total surface fat. It is an aliphatic acyclic hydrocarbon with the empirical formula $C_{30}H_{50}$ and is composed of six isoprene units (Fig. 1). It has been shown by Langdon and Bloch (22) to be an important intermediate in the biosynthesis of cholesterol. Nicolaides and Rothman (23) found that the squalene content of hair fat in the adult is three to four times higher than in children, whereas the reverse is true for cholesterol content. It was further found by these workers and others (24,25)

that human skin incubated *in vitro* can incorporate C_{14}-labeled acetate into fatty acids, sterols, and squalene and that the main site of sterol synthesis is the keratinizing epidermis while the main site of squalene synthesis is the sebaceous gland.

Attempts to assign special roles to squalene other than that of sterol precursor in the metabolism of human skin have so far been unsuccessful (26) as have been hypotheses attempting to relate squalene to human hair growth or balding (27–29)

The cholesterol content of human surface lipid in normal sebaceous gland bearing areas is about 3 to 4 per cent (8 10) More than six times higher values are obtained in lipids from surfaces lacking sebaceous glands such as the soles (30,31) and very much higher values also occur under conditions where scaling is present as the result of accelerated keratinization (32) Furthermore, within limits the longer one leaves surface fats on the skin the higher is their cholesterol content. Marchionini and Ottenstein (33) found that the maximum cholesterol level on the skin surface is reached only 4 to 5 days after a bath Similar findings were reported by Carrié (34) All these points clearly support the conclusion that the major part of the cholesterol and its esters in skin surface lipids derives from keratinizing cells and that the cholesterol content of true sebum is very low It would appear as though cholesterol synthesis by sebaceous cells is blocked at the intermediate squalene stage It is of interest however that under pathological loading of the system with cholesterol the relative and absolute amounts of this material in skin surface fats increases (35) It appears as though sebaceous glands in the presence of an excessive supply of cholesterol can passively take up and excrete it

Other sterols have also been found in human surface lipids. These include dihydrocholesterol and most probably 7-hydroxy cholesterol (36,5) Minute amounts of 17 ketosteroid estrogen and 3-hydroxysteroid have also been reported (37) and evidence for traces of lanosterol has been claimed (38) Traces of other unidentified steroids are also likely present (5)

As concerns straight and branched-chain paraffinic hydrocarbons which were found in varying small amounts in early

studies on surface lipids in man (10,36) it appears that they almost certainly represent contaminants (9) Hougen recently claims to have found polycyclic hydrocarbons in the hair fat of Bantu natives (39) but again the possibility of such being contaminants cannot be rigidly excluded.

The wax alcohols account for about 6 per cent of the total human skin surface fat. They are all primary alcohols and chiefly straight-chain compounds forming a homologous series ranging from C_{14} to C_{28} (10 40) Compounds with odd as well as even numbers of carbon atoms are present, and only about one-fourth of the compounds are unsaturated. Hougen (40) has also found branched-chain alcohols with terminal isopropyl groups of chain lengths C_{18}, C_{21} and C_{23}. It is of interest that free wax alcohols do not occur on the skin surface (9) They are all esterified. It appears that only glycerides are split when surface fat is stored and that fatty acids are not liberated either from waxes or from cholesterol esters.

On the basis of biological effectiveness, ultraviolet irradiated human surface lipid has been known to contain vitamin D Only recently has spectroscopic demonstration of provitamin D in such lipid been made (38) With the exception of traces of vitamin E, the other fat-soluble vitamins, A and K, have not been chemically detected in human sebum (5,8) About 7 to 8 per cent of human hair fat consists of unidentified substances (9). Traces of phospholipid and some phenolic reducing substances account for part of this material

Detailed analytic information on the composition of lanolin or wool fat, which has been used commercially for decades, has also become available only during the past 10 years (8) which is an indication of its complexity Unlike human sebum it lacks triglycerides and has only a trace of hydrocarbons. Instead of squalene it contains 12.5 per cent of isocholesterol which is a mixture of the four terpene alcohols or trimethylated sterols lanosterol dihydrolanosterol agnosterol and dihydroagnosterol Free fatty acids account for only about 10 per cent of the material About four times this amount of fatty acid is present in esterified form with aliphatic alcohols, sterols, triterpene alco-

hols, and alkane-diols (41) The fatty acids of wool fat were examined in detail by Weitkamp (42) and fell into four series (Table II) (*a*) normal C_{1} to C_{34} acids with even numbers of carbon atoms (*b*) alpha hydroxy acids C_{14} and C_{16}. C_{12} and C_{1} and iso-C_{17} have more recently also been added to this series (*c*) iso acids C_{1} to C_{28} even numbered only and (*d*) anteiso acids C_{9} to C_{3} odd numbered only Some unidentified unsaturated acids were also found The aliphatic alcohols in wool fat (43) account for about 10 per cent of the material and

TABLE II F[illegible]tty acid[illegible] Isolated from wool f[illegible]t (12)

Homologous series	General formula		Number of C atoms even or odd	Isolated members of series
1 Normal fatty acid	$CH_3-(CH_2)_{n}-COOH$	4 to 12	even	C [illegible] to C [illegible]
2 2 Hydroxy acids	$CH_3-(CH_2)_{n}-CH(OH)-COOH$	6 and 7	even	C [illegible] and C [illegible]
3 Iso acid[illegible] with methyl side chain penultimate position	$CH_3-CH(CH_3)-(CH_2)_{n}-COOH$	3 to 11	even	C [illegible] to C [illegible]
4 Anteiso acids [illegible]h methyl side chain in ante penultimate position	$CH_3-CH_2-CH(CH_3)-(CH_2)_{n}-COOH$	2 to 13	odd	C [illegible] to C [illegible]

belong to three series (1) normal C_{16}, C_{20}, C_{22}, C [illegible] and C_{24} (2) iso-C [illegible], C [illegible] C_{22}, and C_{25} and (3) anteiso-C_{14}, C [illegible] C_{20}, C_{22} C_{2} and C_{24}. The alkane 1,2-diols (41) with terminal isopropyl groups have chain lengths of C [illegible] C_{20}, C_{22} and C_{2} In addition small amounts of cholesta 3,5-dien 7-one appear t[illegible] be present Cholesterol accounts for another 10 per cent of w[illegible]l fat and dihydrocholesterol for 9 per cent It is clear from these data that lanolin differs rather radically from human skin surface fat Wheatley and James (8) have examined the skin surface fats of common laborat[illegible]ry animals such as the guinea pig mouse rabbit and rat (Table III) In spite of the fact that all are rodents very striking differen[illegible]es in their surface lipid com

TABLE III Skin surface lipids in man and several animal species (8)

Constituent	Man	Sheep	Guinea pig	Mouse	Rabbit	Rat	Ox	Duck	Goose
Fatty acids (free)	28.3	11.0	8.0	7.5	9.0	7.4	5.1		
Fatty acids (combined)[a]	54.6	44.0	49.5	36.7	45.6	51.4	53.4	47.6	47.5
Triglycerides	32.5	0	0	0	0	0			
Unsaponifiable matter	30.1	46.1	44.8	54.6	45.9	41.4	42.7		
Squalene	5.5	0	0	0	0	0			
Hydrocarbons	8.1	1	1.5	1.1	3.3	1.5			
Wax alcohols	6.2	9.0	5.0	5.9	31.0	17.5		48.0	48.0
Cholesterol	4.1	10.0	18.0	4.5	3.5	5.8	14.4	1.4	0.3
Dihydrocholesterol	0.1	2.5							
Lathosterol			1.8	8.1	0.1	4.4			
Other sterols	0.5	1	0.7		0.5	0.2			
Isocholesterol	tr	12.5							
Alkane-1,2 diols	2.0	2.5	5.6	27.5	2	2.9			

[a] triglycerides, waxes, and other esters.

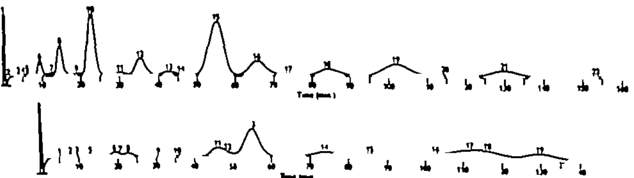


FIG. Gas chromatograms of methyl esters of the fatty acids in rabbit and rat sebum (8)

Analysis of 1.8 mg of methyl esters of the cids present n rabbit sebum. Peaks in order of appearance: (1) air introduced loading column (?) water present in air in (1) (negative peak) (3) n-decanoic acid, (4) branched C_{11} saturated acid, (5) n ndecanoic acid (6) dodecanoic acid, (7) branched C_{13} saturated acid, (8) n-tridecanoic acid (9) branched C_{14} saturated acid, (10) n tetradecanoic cid (11) branched C_{15} saturated acid, (12) n-pentadecanoic acid, (13) h ghly branched saturated C_{16} acid (14) branched C_{16} saturated acid, (15) n-hexadecanoic acid, (16) highly branched C_{1} saturat d acid (17) branched C_{1} saturated acid (18) heptadecanoic acid (19) highly branched C_{1} saturated acid, (?0) mono- nsaturated acid C_{18}, probably oleic cid, (?1) n-octadecanoic acid (22) *highly branched* C_{19} saturated acid Colum temperature 197 length 4 ft. Nitrogen pressure 73.5 cm Hg nitrogen flow rate 100 ml/min. St tionary phase aromatic l b icating oil extract

Analysis of 4.8 mg of methyl esters of the acids present in rat sebum. Peaks in order of appearance: (1) n-decanoic acid (?) branched C_{1} acid, (3) n-dodecanoic acid, (4) branched C_{13} acid, (5) n-tridecanoic acid, (6) branched C_{14} acid (?) mono-unsat rated C_{14} acid (8) n-tetradecanoic acid, (9) branched C_{15} acid (10) n-pentadecanoic acid, (11) branched C_{1} acid (1?) mono-unsaturated C_{1} acid, (13) n-hexadecanoic acid (14) branched C_{17} acid (15) heptadecanoic acid (16) highly saturated C_{18} acid, (17) branched C_{18} acid (18) mono-unsaturated C_{1} acid, (19) -octadecanoic acid

positions were found Even gas chromatograms of only the fatty acid components of these surface fats revealed highly characteristic features for each species (Fig 2) It would appear that study of surface lipids in animals might well prove fruitful in establishing zoological relationships. A curious point in common to all the rodent surface lipids is the presence of lathosterol instead of squalene or isocholesterol (Fig 1) It is of interest that horse sebum contains squalene, whereas the seba of ruminants including sheep goat llama and dromedary contain isocholesterol. The sebum obtained from the unique preen glands of birds contains only a very small amount of sterols (45 46)

It has been postulated that the biogenesis of the various series of fatty acids and wax alcohols in surface fat involves the normal process of acetate addition but that this process may commence upon the carbon skeletons of decarboxylated and deaminated amino acids so that products with odd numbers of carbon atoms could result (5 8) The iso and anteiso series of branched-chain compounds could readily be built by this mechanism upon the skeletons of valine and isoleucine respectively There are of course still very many unsolved problems in the biogenesis of the various components of surface lipids.

Physiologically the amount of sebum delivered to the skin surface depends primarily on three factors. (*a*) the number of sebaceous gland cells per unit area, (*b*) surface skin temperature and (*c*) the emulsifying action of sweating The first of these factors is clearly the most important, and twenty years ago Emanuel (47 48) contended that sebum is excreted alone through the force derived from the proliferation of the sebaceous cells. Miescher and Schonberg (49) brilliantly showed this conception to be true. They measured sebum secretion rates in normal individuals and in those with varying degrees of seborrhea. Then in skin biopsy specimens, they measured sebaceous glandular surface areas relative to total skin area and found a constant ratio between sebum production and glandular surface area in all cases.

Increasing skin surface temperature and sweating increase delivery of sebum over the skin surface by lowering its viscosity

and enhancing its spread over the surface from reservoirs in the sebaceous gland ducts, the follicular canals, and the interstices of the stratum disjunctum of the horny layer (50,51). Sebaceous secretion can be viewed primarily as a more or less continuous process manifesting the differentiation of cells in the sebaceous glands. This process has not been shown to be under any direct nervous control (5). It is of interest that when sebaceous material is removed from the skin surface, fat reaccumulation begins at a rapid rate but then this rate appears to decline (47,48,52–54). Probably the best explanation for this *phenomenon lies in the work of Herrmann, Prose and Sulz*berger (51), who called attention to the role of sebum reservoirs in regulating the amount of sebum on the skin surface when measured by the usual wiping procedures. Others (55,56) have felt that partial plugging of sebaceous ducts with very viscous sebum may actually hinder sebaceous cellular proliferation. This latter view has recently been under strong criticism (57), but the question is not settled. An estimate for a minimum rate of sebum secretion in human skin has been placed at 0.1 microgram per square centimeter per minute (20) or about 12 mg per hour over the whole body surface. The actual excretion is probably much in excess of this minimum estimate.

Factors that regulate sebaceous gland size and development are clearly the determinants of the amounts of sebum excreted. Under ordinary circumstances these prime regulators of sebaceous gland size and activity are endocrine factors. A fact of outstanding importance is the striking pubertal enlargement of these glands in both sexes in man as well as in animals. That male sex hormone plays an important role in this pubertal development has been firmly established for a long time. Along clinical lines Hamilton (58) noted failure of sebaceous gland enlargement in male prepubertal castrate or eunuchoid individuals and Rony and Zakon (59) observed striking enlargement of sebaceous glands in prepubertal boys given injections of testosterone. Numerous animal experiments by many workers including DeGraaf (60,61), Hamilton and Montagna (62), Ebling (63), and Reiss and Gellis (64) have confirmed these

clinical observations, and stimulation of sebaceous glandular growth by androgen was reported in the rat, rabbit, and hamster. In the rat administration of estrogen in unphysiologically huge doses was found by Ebling (63) and by Hooker and Pfeiffer (65) to cause a reduction in size of sebaceous glands and also by the latter workers to counteract the growth-stimulating effect of androgen on these structures.

In females it had generally been assumed that pubertal seborrhea was induced by increased production of adrenal androgens. However this assumption was difficult to accept because male castrates and ovarian-deficient females who do not show this physiological seborrhea have normally functioning adrenal glands. In 1953 Haskin, Lasher and Rothman (66) following up earlier controversial observations (60-63) on the effects of progesterone were able to demonstrate clearly in castrated rats by means of a specially devised histometric method that progesterone as well as testosterone has a striking growth-promoting effect on sebaceous glands. They also found that there was always a constant ratio of sebaceous cell nuclear counts to sebaceous gland alveolar volume indicating that hormone-induced sebaceous enlargement is the result of hyperplasia, i.e. an increase in numbers of sebaceous cells, rather than simply hypertrophy or enlargement of single cells. Clinical observations in man have since then added supporting evidence for the stimulating effect of progesterone on sebaceous glands. These observations include the following: (*a*) the association with luteomas (presumably progesterone-secreting tumors) of seborrhea and acne (67); (*b*) the rough correlation between premenstrual acne and peak levels of circulating progesterone (68); and (*c*) the aggravation of acne as well as its induction by administration of large doses of progesterone. Zeligman and Hubener (69) in 1957 demonstrated this last point particularly well. They administered progesterone to women without previous acne in doses of 50 mg daily for periods as long as twelve weeks and noted that acne was induced in a way closely similar to the acne which can be induced with testosterone administration. Of course, acne vulgaris is not based solely on sebaceous

gland enlargement, but such enlargement appears to be a necessary prerequisite for its development.

A number of years ago in collaboration with Lasher and Rothman I undertook a study of the effect of the pituitary adrenal axis on sebaceous glands in ovariectomized adult rats

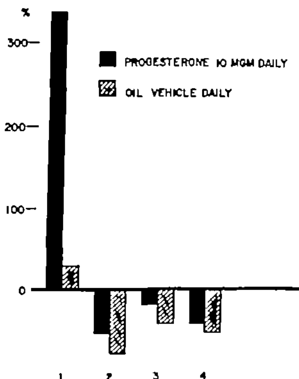


FIG. 5 1 O ariectomy 2, ovariectomy pitu tectomy 3 ov ri ectomy pituitectomy STH 0 1 mg daily 4 ovariectomy p t tec tomy ACTH 1 unit daily

(70 71) The results of the first series of these experiments can be summarized as follows

1 Removal of the pituitary and adrenal glands leads to atrophy of sebaceous glands which cannot be counteracted by progesterone.

2 Hypophysectomy alone leads to sebaceous gland atrophy in similar manner

3. Adrenalectomy alone leads to much less atrophy of sebaceous glands which can be readily overcome with progesterone administration.

4. The stimulating effect of testosterone on the growth of sebaceous glands is greatly reduced in hypophysectomized animals although not totally abolished.

Ebling (72) has confirmed that a pituitary factor is required for testosterone to exert its full action on sebaceous glands.

TABLE IV Types of standard hormones used and their dosage bases

Hormone	Commercial preparation and manufacturer	Dosage basis
Prolactin	Luteotrophin (E. R. Squibb & Sons)	International unit
ACTH	Purified corticotropin-gel (Wilson & Co.)	U.S.P. unit
Pituitrin (oxytocin plus other posterior pituitary activities)	*Pituitrin-S (Parke Davis & Co.)*	*International unit*
Pitressin (vasopression plus antidiuretic activities)	Pitressin (Parke Davis & Co.)	pressor unit
Chorionic gonadotropin (from human pregnancy urine)	A.P.L. (Ayerst, McKenna & Harrison, Ltd.)	International unit
Gonadotropin (from pregnant mare serum)	Gonadogen (Upjohn Co.)	Cartland-Nelson unit (equal to 20 international units)
Gonadotropin (mixture from pituitary and pregnancy urine sources)	Synapoidin (Parke-Davis & Co.)	Synergy rat unit

In the next phase of our work we took up a study of the nature of this pituitary effect and attempted to find out what factor from the pituitary gland must be present in order for progesterone or testosterone to exert their stimulating effects on sebaceous glands. We first tested various known pituitary hormone preparations in hypophysectomized castrated rats for their ability to restore growth responsiveness of sebaceous glands to progesterone stimulation.

Neither ACTH nor growth hormone (STH) were effective

(Fig 3) although physiologically active doses were used as indicated respectively by adrenal hyperplasia and maintenance of good body growth

Table IV shows the various other pituitary and analogous hormone preparations that we also tested

The results of these tests are summarized in Fig 4 It can be seen that pituitrin pitressin prolactin follicle-stimulating

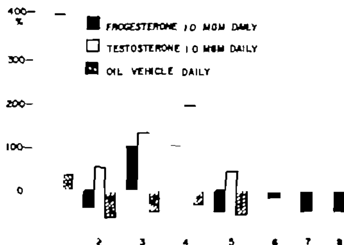


FIG. 4 1 Ovariectomy 2 ovariectomy pituitectomy 3 ovariectomy pituitectomy Synapoidin 1.5 units daily 4 ovariectomy pituitectomy Gonadogen 0.? unit daily 5 ovariectomy pituitectomy ACTH 20 units daily 6 ovariectomy pituitectomy Prolactin 10 units daily 7 ovariectomy pituitectomy FSH units daily 8 ovariectomy pituitectomy Pituitrin S and Pitressin 1 unit of each daily

hormone and chorionic gonadotropin all failed to restore sebaceous gland responsiveness. Thyrotropin though not shown in the figure has also been tested and found inactive By way of contrast the Synapoidin® and Gonadogen® preparations had such activity Gonadogen® is a preparation obtained from pregnant mare serum which presumably contains gonadotropins of pituitary as well as of chorionic origin and Synapoidin® is a mixture of gonadotropins from pituitary and pregnancy urine sources.

In order to characterize further the nature of the pituitary sebaceous gland tropic factor present in these gonadotropic preparations we obtained the cooperation of representatives of Wilson & Co in preparing for us crude fractions from hog anterior pituitary glands.

At first the general fractions shown in Table V were sup-

TABLE V Initial crud fractions tested for sebotropic ctivity

Fraction	General method of preparation
Pit. I	Alkaline extract at pH 8.5 (0.1M NaOH) of fresh hog anterior pituitaries
Pit. II	Alkaline extract t pH 8.5 (0.1M NaOH) of residue left after extraction of fresh hog nterior pit itaries with hot glacial acet c acid
Pit. III	Hot glacial cetic acid extract of fresh hog nterior pituitaries

plied and tested. Their general hormonal natures are shown in Table VI and Fig 5 shows their sebotropic activities. It can be seen that although preparations I and II both had potent sebaceous gland tropic activity preparation II had almost no gonadotropic activity and thus sebotropic activity appears to vary independently of gonadotropic activity

TABLE VI. Gonadotropic nd other normal activities in crude fractions prepared from nterior pituitary glands of hogs (71)

Preparation	Gonadotropic activity (μ/cc)	Other activities
Pit. I	0.110	—
Pit. II	0.036	—
Pit III	0.007	ACTH STH TSH MSH

The work of purifying and further characterizing this pituitary sebotropic factor is still in progress and present evidence indicates that activity resides in a fairly large protein molecule rather than in a small peptide. In 1957 the weight increase of

preputial glands in hypophysectomized castrated adult rats given standard doses of progesterone was found useful in assaying for sebotropic activity (73)

The applicability of these results to man of course still has to be shown Nevertheless, it is interesting to speculate should

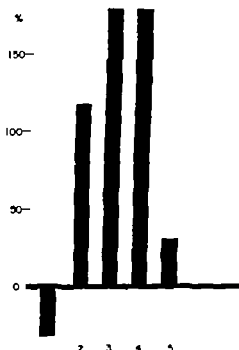


FIG. 5 1 Saline 2, Gonadogen 0.5 unit daily 3 Pit. I ? cc daily 4 Pit. II 2 cc daily 5 Pit. III 2 cc daily In all groups the rats were ovariectomized, pituitectomized and given progesterone 1 0 mg daily

these experiments be applicable to man about a possible explanation for the seborrhea associated with some types of mid brain damage such as occur in postencephalitic syndromes. Such seborrhea based upon sebaceous gland enlargement could conceivably result from release of normal inhibition of pituitary output of sebotropic hormone

Finally as regards other endocrine influences on sebaceous

glands it seems that thyroidectomy in young animals results in regression of the entire pilosebaceous apparatus (74) Clinical observations on the effect of thyroid substance on seborrhea and acne are poorly controlled and controversial

As concerns nutritional influences sebaceous glands may be affected late in the course of many nutritional deficiency states but only riboflavin and zinc deficiencies affect sebaceous glands early in the course of the deficiency In the rat, in zinc deficiency spectacular enlargement of sebaceous glands has been reported by Follis, Day and MacCollum (75) In riboflavin deficiency early disintegration and atrophy of sebaceous glands was reported by Sullivan and Nicholls (76) A curious fact reported by Smedley McLean and Hume (77) is that cutaneous lipids increase in amount and retain their content of essential unsaturated fatty acids in rats kept on a fat free diet. This has led to speculation that essential fatty acids may possibly be synthesized by sebaceous glands (5) Finally it is of interest to note that in rats forced feeding of unphysiologically large amounts of fat causes sebaceous gland enlargement with greatly increased excretion of sebum (78–80) Indication of a similar phenomenon has been reported in man (55) It has been suggested that sebaceous glands can pick up and excrete lipids when offered to them in excessive amounts by mechanisms which may bypass the usual metabolic pathways for sebum formation (5) Definitive studies to confirm this suggestion have yet to be done

REFERENCES

1 Schaffer J *Z. mikroskop-anat Forsch* 22 579 (1930).

2 Petit, A and Geay F *Bull muséum nat hist nat (Paris)* 11 117 (1905)

3 Montagna W *The Structure and Function of Skin* Academic Press, New York 1956. Pages 281 286 328.

4 Melczer N and Deme S. *Arch Dermatol u Syph lis* 183 388 (1913).

5 Rothman, S. *Physiology and Biochemistry of the Skin* University of Chicago Press, Chicago, Ill., 1954.

6 Wheatley V R *Livre Jubilaire 1901 1951 de la Société Belge de Dermatologie t de Syphiligraphie* Imprimerie Medicale et Scientifique, Brussels, 1952 Pages 90-102.
7 Wheatley V R *St Bartholomew s Hosp J* 5 5 (19 3)
8. Wheatley V R. *Am Perfu ner 68* 37 (1956)
9 Nicolaides, N and Foster R C., Jr *J Am Oil Chemists Soc 33* 404 (1956)
10 Nicolaides, N and Rothman S *J Invest Dermatol* 21 9 (1953)
11 Kung, S K. *J Natl Cancer Inst* 9 435 (1949)
12. Montagna, W and Hamilton, J B. *Federation Proc* 6 166 (1947)
13 Nicolaides, N and Wells, G C *J Invest Dermat l 29* 1-3 (1957)
14 Weitkamp, A W Smiljan c, A M and Rothman S *J Am Cl em Soc 59* 1936 (1947).
15 James, A. T and Wheatley V R *Biocl em J 63* 269 (1956)
16 Burtenshaw J M L. *J Hyg 4* 181 (1942)
17 Miescher G Lincke H and Rinderknecht P *Dermatol g a 109* 65 (1954).
18 Rothman, S Smiljanic, A M Shapi ro, A L., and Weitk mp, A W *J Invest Dermatol 8* 81 (1947)
19 Jones, K K. *Science 111* 9 (1950) *Qua t Bull N thwe tern Univ Med Scl ool* 4 2 3 (1950)
20 Jones, K K Spencer M C., and Sanchez S. A. *J Invest Dermatol. 17* 213 (1951).
21 Herrmann F Harber L. C., Scher R and Mandol L. A M A *Arch Dermatol* 76 282 (1957)
22. Langdon R G and Bloch, K *J Bi l Che n 200* 135 (19 3).
23 Nicolaides, N and Rothman S *J Invest Dermat l 19* 389 (1952)
24 Nicolaides, N and Rothman, S *J In est Dermat l* 125 (1955)
25 Nicolaides, N Reiss, O K., and Langdon R G *J Am Ch m Soc* 1535 (1955)
26 Srere P A., Chaikoff I L., Treitman, S S., and B rstein I S. *J Biol Ch m 182* 629 (1950)
27 Flesch P *Proc Soc Exptl Biol. Med* 6 801 (1951).
28 Bloom, R E., Woods, S. and Nicolaides N *J In e t De ma t l* 4 97 (1955).
29 Boughton, B Mackenn R M B Wheatley V R and Wormall A *Biochem J 66* 32 (19)
30 Eckstein, H C and Wile U *J Biol Chem 69* 181 (1926).

31 Engman, M F and Kooyman, D J *Arch Dermatol and Syphilol. 29* 12 (1934)
32. Marchionini A., Manz, E., and Huss, F *Arch Dermatol u. Syph lis 1 6* 615 (1938).
33 Marchionini A., and Ottenstein, B. *Klin Wochschr 10* 969 (1931).
34. Carrié, C. *Arch Dermatol u Syphilis 188* 241 (1949-50)
35 Rothman S., and Schaaf F In Jadassohn *Handb d Haut u. Geschlechtskr* 1/2. J Springer Berlin, 1929 Pages 161-377
36. MacKenna, R. M B Wheatley V R., and Wormall A. *Biochem J., 52* 161 (1952).
37 Dubovil M L *Ukrain Biokhim Zhur 26* 279 (1954)
38. Boughton B., and Wheatley V R. Unpublished.
39 Hougen, F W *Chem & Ind (London) 1954* 92.
40. Hougen F W *Biochem J 59* 302 (1955)
41 Truter E V *Quart Rev Chem Soc London 5* 390 (1951)
42. Weitkamp A. W *J Am Chem Soc., 67* 447 (1945)
43. Murray K. E., and Schoenfeld, R. *J Am Oil Chemists Soc 29* 416 (1952)
44. Horn D H S., and Hougen F W *J Chem Soc. 1953* 3553
45 Hou, H C. *Chinese J Physiol* 345 (1928)
46. Weitzel G and Lennert, K. *Z. physiol. Chem Hoppe-Seyler's 288* 251 (1951)
47 Emanuel S. *Acta dermat venereol. 17* 444 (1936).
48. Emanuel, S. *Acta dermat venereol. 19* 1 (1938).
49 Miescher G and Schonberg, A. *B ll schweiz. Akad med Wiss 1* 101 (1944)
50. Herrmann F and Prose, P H *J Invest Dermatol 16* 217 (1951)
51 Herrmann, F Prose, P H and Sulzberger M B. *J Invest Dermatol 18* 71 (1952).
52. Schur H and Goldfarb L. *Wien klin Wochschr 40* 1255 (1927)
53 Serrati B. *Riv patol nervosa 52* 377 (1938).
54 Zehender F and Dunner M *Dermatologica 93* 35 (1946)
55 Dunner M *Dermatologica 93* 219 (1946)
56. Butcher E. O and Parnell J B *J Invest Dermatol 10* 31 (1948)
57 Kligman A. M and Shelley W B *J Invest Dermatol 30* 99 (1958)
58. Hamilton J B *J Clin Endocrinol 1* 570 (1941).
59 Rony H R and Zakon, S. J *Arch Derm t l Syph lol 48* 601 (1943).
60. De Graaf H J *Acta brevia Neerl 1* 67 (191).

61 De Graaf H J *Acta brevia Neerl* *13* 77 (1949)
62. Hamilton J B and Montagna, W *Am J Anat* *86* 191 (1950).
63 Ebling, F J *J Endocrinol* *5* 297 (1948)
64 Reiss, F and Gellis S. *J Invest. Dermatol.* *12* 159 (1949)
65 Hooker C. W and Pfeiffer C. A *Endocrinology* *32* 69 (1943)
66. Haskin D Lasher N and Rothman S *J Invest Dermatol* *20* 207 (1953)
67 Selye, H *Textbook of Endocrinology* 2nd edition Acta Endocrinologica Montreal 1949
68. Aron-Brunetière, R. *Brit J Dermatol* *65* 157 (1953)
69 Zeligman, I and Hubener L. F *A.M.A Arch Dermatol* *76* 652 (1957)
70 Lasher N Lorincz, A L. and Rothman S. *J Invest Dermatol* *2*. 25 (1954).
71 Lasher N Lorincz, A L., and Rothman, S. *J Invest Dermatol* *24* 199 (1955)
72. Ebling, F J *J Endocrinol* *15* 297 (1957)
73 Lorincz, A L., and Lancaster C *Scien e 1 6* 1 1 (19 7)
74 Jurenka W *Z Zücht Reihe B* *7 Tierzücht Zuchtungsbiol* *31* 373 (1935)
75 Follis R. H Jr Day H G and McCollum, E. V *J Nutrition* *2*. 223 (1941).
76 Sullivan M and Nicholls, J *J Invest. Dermatol* *4* 181 (1941)
77 Smedley-MacLean I and Hume E. M *Biochem J* *35* 990 (1941).
78 Schmidt, M B. *A ch pathol Anat u Physiol Virchow s* *53* 432 (1921)
79 Klinge F and Wacker L. *Krankheitsforsch* *1* 257 (1925)
80 Suzuki S. *Japan J Derm tol Urol* *40* 903 (1936).

Discussion

Dr. Van Scott (1) Is it known clinically that gonadectomized females do not develop acne as do gonadectomized males? (2) A pharmacist recently gained notoriety on a product which contained tin on the basis that t n inhibits boils Is there any evidence that tin really causes a decrease in the size of sebaceous glands?

Dr. Lorincz The tin story is a very old one and several decades ago tin was considered good treatment for acne It is however highly toxic and furthermore wa also shown to be ineffecti e As oncerns gonadectomized females not ha ing a ne I do not know f ny clear-cut data on this point. We have recently seen a ase where

ovarian deficiency appears to have developed and in which acne has continued, but all details of the endocrine status of this individual have yet to be worked out.

DR. SULZBERGER It has been observed that the metal vanadium will inhibit the biosynthesis of cholesterol When administered to animals, vanadium compounds will afford a decrease in blood cholesterol levels. Recently the investigator most interested in this phenomenon, Dr G L. Curran of Kansas City observed blood cholesterol decreases in volunteer medical students after the administration of a nontoxic vanadium compound. All the subjects were young adults. I think that it might be profitable to study the effect of this metal on skin lipids, including cholesterol.

DR. ROTHMAN Was your question in reference to primary amenorrhea, Dr Van Scott? Women with aplastic ovaries do not develop acne. They are like hermaphrodites or eunuchoid males in that they never develop acne.

QUESTION If such women are given progesterone, will they develop acne?

DR. ROTHMAN This has not been done. We tried very hard to get such patients from our gynecologists, but they are so eager to give them stilbestrol to get them going that it is hard to persuade them to make a clean experiment. The Zeligman experiments, which were quoted by Dr Lorincz, were done on normal females.

Stannic chloride injections in furunculosis have been absolutely valueless, and also valueless in acne. I think it was one of those nicely built up therapeutic illusions in diseases which one treats locally anyhow and therefore they improve.

DR. BLANK. I hesitate to ask permission to discuss a very small point in Dr Lorincz's very complete and logical presentation, but it is a point that has been made several times and I wish it could be clarified. I refer to the physical state of the lipids on the cutaneous surface. It has been said that they are present as an emulsion. What is the composition of this emulsion? Is this an emulsion of oil and water and if so is it oil in water or water in oil? Personally I doubt that it is either If it is oil in water the water must evaporate very quickly if it is water in oil, the water will still evaporate but more slowly I think early work of Lustig and Perutz, which may not have

G L. Curran. Effect of certain transition group elements on hepatic synthesis of cholesterol in the rat. *J Biol Chem* 210:765 (1954).

G L. Curran and R. L. Costello. Reduction of excess cholesterol in the rabbit aorta by inhibition of endogenous cholesterol synthesis. *J Exptl. Med.*, 103 49 (1956).

D L. Azarnoff and G L. Curran. Site of vanadium inhibition of cholesterol biosynthesis. *J Am. Chem Soc.* 79:2968 (1957)

been confirmed showed that two immiscible oil phases were present. If Dr Lorincz has an opinion about the physical state of the surface lipids, I would like to hear it.

DR. LORINCZ I would say the surface film is probably an oil-in-water emulsion. Of course exactly how one is going to picture such an emulsion when it occurs on a water-imbibing surface spread as a thin film is perhaps where we get into difficulty

DR. SULZBERGER I wish Dr Herrmann were here to answer this question because he has done all the work which forms the basis for my reply According to his work, and this is done by lipid staining and other things, there is a remarkable capacity reciprocal capacity of the lipids and the watery constituents on the skin surface to enter into emulsification with each other In fact, it is so strong that if you put the sebum or the surface lipid, and sweat together they emulsify without any agitation on a plate at once. There is something even more remarkable than that Although the lipids from A with the sweat from B will emulsify sweat from B will emulsify lipids from B even better In other words, there is individual adjustment and individual capacity to mutual emulsification of a person own sweat with his own lipids which is stronger than if he used others. Then the question of whether it is oil in water or water in oil—according to Herrmann's work, it can be either depending entirely upon the amount of water that is being delivered. You can transform it from water in oil to oil in water as soon as there is more fluid, liquid aqueous phase on the skin surface

DR. MARZULLI (Army Chemical Center) How do the chimpanzee and monkey compare with man regarding surface lipids?

DR. LORINCZ The surface lipids of these animals have yet to be collected and analyzed in detail

PATHOGENETIC, THERAPEUTIC, AND COSMETIC CONSIDERATIONS IN ACNE VULGARIS

MARION B SULZBERGER

Department of Dermatology and Syphilology New York University Post-Graduate Medical School New York University Bellevue Medical Center New York

Dermatologists and non-dermatologists as well know that acne is a disease of the very highest incidence, and also that it is a very destructive disease But one of the very first things that I have learned in thinking about acne vulgaris relates to a common fallacy of medical statistics. One cannot find out the prevalence of a disease particularly a disease such as acne by studying any figures that are available in the records of epidemiologists. One cannot find out the prevalence of acne from the records of the autopsy table or from the files of pathological laboratories. And more important one cannot find out about the prevalence of acne vulgaris from insurance company statistics or from the attendance figures in clinics hospitals, or doctors private offices. These last named show only the prevalence or numbers of those who seek relief who have recourse to medical aid for controlling their disease Such figures are of course very misleading They are misleading as far as actual prevalence of acne is concerned as far as age of onset is concerned and as far as the sex distribution is concerned—for very obvious reasons. For instance if one tries to discover the sex distribution one finds at once that many more females than males with acne appear in the clinic records and in the case files of doctors offices That is simply because their beauty their pulchritude the appearance

of their skin are far more important to the females of the species than to the males.

Perhaps the first available accurate figures as to the prevalence of acne vulgaris came from the work of Bruno Bloch which was carried out at about the time that I was an assistant in his clinic. It was reported and published in 1930 and 1931 Bloch examined 4 191 school children for the presence of acne. They were about evenly divided between girls and boys. The age range was from 6 to 19 years. He found out that at the age of maximum prevalence which was at 17 years in the females and at 18 years in the males 96 7% of the girls had acne and 99 4% of the boys had acne These figures refer to acne vulgaris in its widest sense Five to twenty comedoes or more was considered by Bloch to be a clinical manifestation of acne and his figures included these mild cases as well as papular pustular acne or all the more severe forms. Thus, as expected the actual prevalence is tremendously high. But quite contrary to what one might hav expected from medical records, one finds that the prevalence in males is slightly higher than in females. Moreover the severe cases were much more common in males than in females. They reached maxima of 57% in the males at 19 years as compared with only 22% in the females of 18 years—according to Bloch s criteria for severity I think that this finding corresponds to and emphasizes what Rothman reported about the effects of testosterone and progesterone Testosterone is likely to be a stronger acnegenic agent than progesterone for the testicular hormone was the most powerful of the hormones studied in producing sebaceous gland hyperplasia in experimental animals I think that this finding is borne out also by the growth of the hair on the trunk and face and the enlargement of the piloseba ceous apparatus at puberty These are all consistently stronger in the male than in the female

But acne vulgaris is not only a disease of the very highest incidence and therefore of universal concern but also an im

Bruno Bloch Metabolism, endocr ne gland nd ski diseases, with special referenc to cne ulgar nd xanthoma *Brit J Dermatol Syphilis 43* 61 (1931)

portant disease because of the tremendous amount of anguish that it produces. It is a serious disease despite the fact that super ficial consideration seems to deny it As Dr Rothman once expressed it so aptly One must remember and consider most seriously those diseases which do not end life but which ruin it. And acne is a particularly pernicious disease because it starts at such a bad time a bad time for the patient and for his family It comes just at the time when the human being is most inse cure, when he is most labile in his emotions, when he is trying to find his niche—his level socially economically and sexually

It comes at the very worst time of life in so far as its impact upon the disposition, the personality emotions, and psyche of the individual is concerned. Acne appears generally at precisely the age when personal appearance is naturally of paramount importance. Fortunately later in life one need not depend so much upon one s looks for establishing one s place in the world and society but the adolescent still must and still does. And then the exacerbations of acne the pimples come not only at unpredictable times, but apparently at the most inopportune moments. Just when the boy or girl is about to have an inter view to get into a school to make a club or to get into college or when the boy has the heaviest date with the best girl or the girl the most important party or dance, the acne seems to be at its worst, and to break out with fresh seemingly malevolent, force. So the disease often really interferes with the adolescent s getting into a school or fraternity getting a job or a life partner Then again acne vulgaris strikes at the very worst sites. It strikes just in those places that can t be hidden at the face and at the décolleté areas in the girl

Still another point makes acne a ruinous disease this is based upon certain ideas firmly fixed in many lay minds. As far as I can ascertain from ancient times right up to the present some how or other acne has been erroneously connected with ideas of dirt contagion sexual abberations (either excesses, or absti nences, or inadequacies) and with faulty and filthy habits of all kinds. This situation leads to tremendous conflict between parents and children more than is the case in any other disease

One regularly sees the adolescents coming into the physician's office accompanied by their parents and *sometimes by their* grandparents as well. Almost immediately one perceives the tremendous guilt feelings associated with these pilgrimages. The parents blame themselves or the children. *Often they blame or* try to blame, the acne upon something that the children are doing or have done. They tell the doctor that the outbreaks come from not sleeping enough or *sleeping too much*, *from not* going out enough or from going out too much, from not drinking, or from drinking too many cokes, from smoking or from studying, from washing or from not *washing*. *Everything* the child does or does not do is wrong. They keep picking and nagging. Often the child in turn quite shrewdly sees that the parents too have had some acne (because acne certainly is a familial disease). So the patients blame their troubles on their mothers or their fathers. They say to their parents, "Your face is all marked up, and now you have given it to me," and the parents often believe this and must compensate in some way for their guilt. All this emotion quite often leads to open conflict in the physician's office. One hears loud and angry words, encounters tears and tension in the doctor's office more often than occurs in any other disease I know. Acne is, in these respects, a most malignant disease, an almost insupportable disease, in that it leads to many almost insupportable situations.

I would say also that acne vulgaris is a somato-psychic disease par excellence. Acne offers the most instructive illustrations of the ways that a physical disease affects the mind, the mentality and the personality of the individual. When one considers that this disease will usually last for a decade at least, and maintain its severe form for 10 years or more in many cases, one can see how it must be capable of leaving its permanent scars not only upon the skin but also upon the psyche and personality of the affected youthful individual. In view of this, it is very gratifying to be able to state that dermatologic treatment of this disease has improved tremendously in the last decade. Perhaps our therapy has improved here as much or more than in any other such common disease. Our methods of treatment of juve-

nile acne have really made great advances We can now keep these individuals presentable while nature is curing the disease —acne juvenilis is self limited I shall come back to that later Only a very small proportion of cases of acne remain clinically active after the early twenties. The real clinical decade of acne is from the age of about 15 to about 25 It usually starts and stops within that span I think at this moment it should be said that this is one of the first facts that should be explained to the patients and to their parents Because they must not get the idea that one can give them a shot or two or a miracle drug or a few ray treatments or whatever it may be and produce a *cure* What the trained physician is able to give them is a form of manage ment which will lead to what I have called "*Morbidistasis* that is a method of producing not a cure but an arrest or suppression of the morbid process—in analogy to what one does in bacteriostasis fungistasis etc.

My next remarks may be considered most unscientific, but the practical considerations and the truth compel me to discuss treatment in the way that I am going to It may be unscientific to give more than one remedy and to approach the treatment of a patient s disease from many different angles at once because one cannot then find out what each of the factors that one is introducing is actually doing or has done. From that point of view such polypragmatic practice is unscientific. But I would emphasize that the best chance of helping patients with certain diseases (and acne is a superb example of this) is to administer treatment from every possible practical angle and to hit at every link of the pathogenetic chain which leads to the disease. I shall speak later about the various possible links in this chain of causation about the multitude of different factors which in their conjunction and in their addition perhaps even in their synergism will lead to the production of acne lesions.

Figure I shows what a serious cosmetic problem acne can be—a severe case of acne with tremendous cysts and crusts and discolorations which cover the patient s face When this happens to a young man it is a dreadful cross for him to bear and for a young girl it is even worse

Figure 9 shows the back of the same young man who was on Guam and suffered from a *tropical* form of acne Rare cases are as severe as this one and some are even more severe In military personnel *this degree of tropical acne constituted not* only a cosmetic defect but also a disability Men like this could not carry a pack could not wear a uniform could not go into



FIG. 1 Example of severe acne as seen frequently in humid tropics and occasionally in temperate climes [From Sul berger nd Witten Hormones and acne vulgaris. M d Cl N Am 35 5?3 (19 1)]

the showers with the other men. (As high as 70% of all individuals being sent back from the Pacific area during certain periods of World War II were being sent back because of this form of

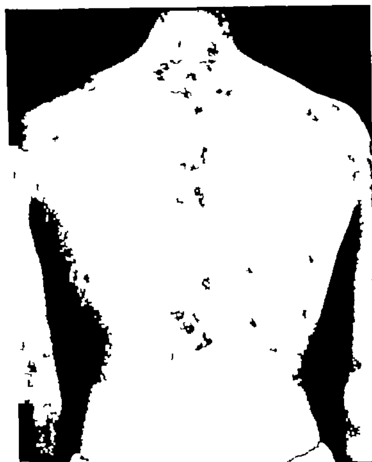


FIG. _ Back of same patient as in Fig 1

tropical acne) This severe form can also occur in peacetime and temperate climate

Figure 3 is a diagram of one chain of causation This is a schematic incomplete and by no means all inclusive representation and not necessarily the only chain of pathogenesis of acne

vulgaris but it represents one possible pathogenetic chain and a common type Here the primary stimulus is the androgenic hormones, perhaps progesterone *Secondly the target organs or* organs of response are the susceptible pilosebaceous structures. Without these two there can be no acne vulgaris and they are really its basis and therefore these two links are drawn larger than the others. Very often nothing much happens in most cases from just these two factors alone. There may be a *little* acne

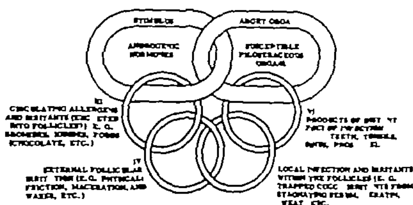


Fig. 8

perhaps the mildest form of 5 to 20 comedoes that Bruno Bloch described and which has such high incidence that it is almost a physiologic happening and scarcely a disease However when one adds to these two fundamental links one or more of the other links then one can complete a chain which leads to manifest disease including the terrible disfigurement of the degree and type shown in Figs. 1 and 2 Now therapy in its polyvalent form which I think its most effective form should be directed against everyone of the links of the chain shown in Fig 1 and against any other links if they exist and one can find them.

What should one do about the hormonal link? In females one can give the antagonistic hormones the estrogenic hormones.

We usually give them monthly for several days before menses. With proper dosage and form they are of some help and entirely safe to give in otherwise healthy young females.

What can one do about the target organ? Here the dermatologists have concentrated most. We can treat the plugged pilosebaceous apparatus and apply medicaments directly to the susceptible pilosebaceous organs (because not all these organs are susceptible). We know that only a certain number of hair follicles and only the hair follicles in certain areas are susceptible to the acne process at any given moment. The main thing here is a measured peeling of those follicular openings in order to keep them patent. That can be done physically and chemically by washing, by abrasives, by resorcin and sulfur combinations, by other physical and chemical peeling agents, such as carbon dioxide snow or salicylic acid or beta naphthol. Moreover the hyperactivity or rather the hypertrophy of the pilosebaceous organs and of the keratinization process can also be reduced by carefully administered x-rays. We know now that this should be reserved for the cases that have proved refractory to other forms of treatment. Nevertheless in the severe cases of acne this disease is so ruinous that all safe methods must be applied. Certainly careful x ray treatment by qualified skin specialists today is eminently safe. I think the indications for x ray in certain cases of resistant acne are just as compelling as they are in certain skin cancers.

As another link in the chain we find that into this occluded follicle all kinds of things can be excreted circulating allergens and irritants bromides, iodides, and derivatives of certain foods (e g chocolate shell fish nuts). Obviously here the problem is to eliminate these acnegenic exposures from the diet and from medication.

External physical and chemical agents that produce acne by increasing the plugging and the irritation of the follicles must be excluded not only the chlorinated diphenyls and oils, but other things found to be offenders in the particular case—friction maceration a fur piece a wool garment a girdle a hair lacquer a pan cake type of make up a tar-containing oint

ment etc. All such things will sometimes produce acne in susceptible follicles and these too must then be sought and excluded.

As still another link we find something very important and relatively new which has improved our management of acne tremendously. We used to think that infection played a very minor role perhaps it does. Nevertheless one of the very best antiacne therapies is to give systemic antibacterial agents consistently for as long as is necessary during the existence of the acne, in the proper circumstances, and with proper regard for the responses and hypersensitivities of the individual patient and always with administration of the smallest morbidistatic doses as well as with the necessary regular examinations precautions and adjuvants of vitamins. Circumstances will determine whether one gives Achromycin Comycin Mysteclin Erythromycin or penicillin or sulfonamides by mouth. The last two are much cheaper and in some cases just as effective as the more expensive antibiotics. This therapy may perhaps act against the local and trapped microorganisms in the occluded follicles, or it may be directed against microorganisms lurking in distant foci of infection the products of which may come to and empty into the occluded follicle by way of the blood stream and by excretory and sebaceous and horny secretory processes. I am sure that this happens occasionally and that after eliminating a focus of infection at a distance one can sometimes clear up an acne that one could not clear up before.

There are of course other links, such as general hygiene and habits, and perhaps even tension fatigue and the psyche involved in producing exacerbations of some cases of acne. These are in my opinion among the smaller and less commonly important links in the chain.

So much for logical therapy directed against the various links of the pathogenic chain of active acne—now let us turn to its sequelae. You all know that among the sequelae of acne are various degrees of scarring. The severity of the scarring does not always go parallel to the severity of the active lesions. Often it does, but not necessarily. It is not an obligatory sequence. Some

people have relatively severe acnes with little or no scarring, and vice versa. We don't know just why. However, I have observed something but I have never found it published or discussed. It is this: when a person has chicken pox, apparently one skin area forms pitted scars more commonly than any other—that is the mid forehead. Thus there seems to be both a local and an individual susceptibility to pitted scarring too, just as there is to keloid formation, although the susceptible individuals and areas are of course not the same ones.

What can be done about the acne scarring? I think this belongs to the dermatologist's management of acne just as does all other minor surgery: the opening of the plugged follicles, the evacuation of cysts and so forth, the injection of antibiotics, corticosteroids, etc., into the cysts; all these must be done according to the judgment of the treating physician. The same applies also to simple removal of comedoes. Usually this is not necessary with modern treatment, but in some cases it still is.

The treatment of scarring is really of two kinds. One is the peeling to various depths, from more superficial peeling with phenol, resorcinol, etc., down to the very deepest form that dermatologists use today, so-called dermabrasion or plastic planing. This was introduced by Kromayer and was reintroduced, developed, modernized, and made popular by the work of the late Abner Kurtin. This form of deep scarification and peeling, as compared with the sandpaper treatment, has the advantage of being done without a general anesthesia. It also has the advantage of being an office procedure. However, in our patients with acne scarring we find that in only about 1 case out of 7 are the conditions suitable for such a procedure. There are many contraindications which we observe. These have been written about and published in many places. Although dermabrasion is the best available method for deep pitted scarring, the treatment of the hypertrophic scarring which occurs in acne is very similar to the treatment of keloidal scarring and hypertrophic scarring in general, with the modern methods of various injections locally, hydrocortisone injection locally, and especially x-rays. None of these is sufficiently satisfactory. Localized repeated

freezing of the scars with CO_2 with pressure is another way of treating the hypertrophic scarring and *perhaps one of the best*. These methods in some cases will produce a certain degree of improvement. None of them is good enough in my opinion or in my hands.

In conclusion I would like to reemphasize my concept that under clinical conditions the acne lesion occurs only in anatomically or physicochemically or immunologically susceptible pilosebaceous organs. The greater the force and number of acnegenic stimuli (external and internal) to which a person is being exposed, the greater the number of follicles which will develop clinical acne lesions. I also incline toward the hypothesis that ordinary juvenile acne burns itself out, goes on to clinical cure, becomes inactive and quiescent, once all the pilosebaceous organs that were susceptible to the *prevailing level* of hormonal, infectious, and other physicochemical acnegenic stimuli *have* become resistant—have *lost* their previous relatively high level of susceptibility. This susceptibility may be lost in each particular target organ when that particular gland and follicle has been destroyed, or its orifice has been widened, fixed, or scarred, or when it has been immunologically or otherwise altered by a previous acne lesion.

This presentation has been fragmentary, but I hope that I have shown that acne can be a devastating disease, that dermatologists have learned much about its management, and that we can help most cases. One thing physicians as well as patients and their families should remember: nothing could be more erroneous on their part than to say that this is just a few adolescent pimples, that nothing can be done, and that nothing need be done. A great deal needs to be done, and a great deal can be done for almost every sufferer from acne today.

Discussion

DR. ROTHMAN: I think there was a comment that very little was said about the role of bacteria in inflammatory acne lesions and what was said was more or less contradictory. On the one hand it

was pointed out that leucotaxis occurs without demonstrable bacteria in the lesion On the other hand your therapeutic suggestion was that antibiotics be given. Also I would like to ask if you have ever used staphylococcus vaccines, which many people think are effective? Would you tell us your opinion on the role of bacteria? Is it always secondary? If you can show pathogenic bacteria by culture, do they play a role or not?

DR. SULZBERGER. That is a long question and I am afraid I do not have all the answers. First of all, I shall try to answer about vaccines. I do not use vaccines any more in any significant number of cases. Perhaps for the last year or so I haven t had to use such a vaccine in a single case of acne simply because the action of other treatments, especially the antibacterial medications, seems to be so much quicker and so much more effective A bad case of acne that responds well to antibiotics by mouth will clear up almost 75–90% within a week to ten days and will maintain this improvement through the entire years of the course of the acne sometimes with very small daily doses of the antibiotic. An example would be the case in which 4 × 250 milligrams of a wide-spectrum antibiotic a day is given to start with after a few weeks to a few months 125 or 100 milligrams can be given a day and then 100 milligrams every second day during the entire course of the acne, and this can keep the disease under control and the patient practically free of lesions. So many cases react so well to this kind of treatment that one need not use vaccines. Of course one has to select the antibiotic. Everyone with whom I have discussed this has said maybe it is an entirely different form of mechanism Perhaps the antibiotic is acting upon microorganisms. But perhaps, on the other hand the antibiotic is not acting as an antibacterial agent at all but is acting as t does when it promotes growth and other things. The argument against the last named hypothesis is that many cases of acne do well with certain antibiotics nd not with others which seem to have the same sort of action in stimulating growth in animals. Moreover many cases will do well also with sulfonamides, which have in common with antibiotics the ntibacterial effect but not the growth stimulating effect, as far a I know So I think the response of acne to antibiot cs pe ks in favor of a more important bacterial role than we thought before Because it is undeniable that many of these pustules are sterile by ll methods that we use today to culture them it is hard to explain these two things. But perhaps these ntibiotics act upon distant foc of bacterial infection and not on the local pustule

DR. ROTHMAN You had wr tten p distant foci as being one link in the pathogenesis of a ne Do you seriously believe that if you

pull a tooth or take out the tonsils, or take out the gall bladder that you influence the course of acne?

DR. SULZBERGER I don't only seriously believe it, I feel I know it. I know it to hold true in some cases. What the mechanism is whereby the sequence is produced, what the relationship is between the cause and effect and how the removal of a focus does it, I don't know. I do know that I have seen chin acnes in women that could not be cleared up and did not clear up until an infected tooth was pulled. The tooth might have been one with just a small apical abscess and after its removal the acnes responded very well to acne therapy but not before. There is no doubt that I have seen such cases, not one but several. I don't know if anyone else here has had this experience.

DR. BENINSON (Ford Hospital, Detroit) We had a woman in her late twenties who had acne primarily on the right side of her face which was resistant to all modalities of treatment until she had a lesion around the anal crypt cleared up by a proctologist, whereupon this process immediately resolved itself.

DR. ROTHMAN Wouldn't you agree that acne has a quite special form which almost looks like a different disease? This is a form we call acne conglobata. Its characteristic is that it does not respect the regional limitations of acne vulgaris. Wouldn't you agree that all the tropical cases you have shown do belong in the acne conglobata group? What is characteristic for acne conglobata is that the great majority of lesions do abscess, they do break down, they do form undermined ulcerations with slow healing tendency and ugly large pitted scars. In true acne vulgaris we do not see eruptions on the nape of the neck, on the extremities, etc., as you have shown us.

DR. SULZBERGER What Dr. Rothman said is right. But I interpret acne conglobata as being a variant, a severer form of acne vulgaris, because it is associated with acne vulgaris. That is why I discussed the boy who had acne vulgaris on the face when he came to Guam because he had never "immunized" the pilosebaceous organs by previous acne in that area. Those pilosebaceous organs were still susceptible. Then he got the conglobata form on his back, chest and arms. Whereas many of the older men had previously had acne vulgaris of the face, very often one could objectively prove that they had had it by the facial scars. These men did not get their tropical acne on the face but got it on the arms, chest and back. One sees these cases not only in the tropics but also here.

DR. ROTHMAN In what sense do you speak of immunity in this connection? Would you call it immunity that the prostate gland grows to a certain size and then stops growing? The same thing happens with all the adolescent changes. There are adolescent changes which do come to a leveling off. Our voice does not get deeper and

deeper with our age. It gets deeper to a certain degree and then it levels out.

Dr. Sulzberger. What Dr Rothman said is correct. What produces this arrest of any cutaneous disease phenomena we don t know but there must be forces that do it. This is an interesting thing for instance, with ringworm infections, why do they form rings of a certain size? Why doesn t each ring grow until it covers the whole body? In other words, one cannot just accept this stoppage. There must be an explanation for it too, and in the case of ringworm Stephan Epstein and others have shown it to be based on local acquired immunity If you now ask me how I use the word immun ty I use it in its plain English sense meaning the state of being immune.

Dr. Gerow (Head of the Science Department of American High School) I would like to point out one thing that was missing on the board there a missing link, and that is nutrition. I think that we ha e omitted a very important thing in nutrition and that is milk. We ha e milk in everything today milk in hot dogs, milk in cake, milk in bread. People are preaching milk Our youngsters are speeded up. Their growth is from three years ahead of what they sed to be. They are growing ahead sexually Their metabolism is thrown out of kilter The milk is unbalanced. It has a high calcium and low phosphorous content. It is low in trace minerals. Dr Stark of Harv rd said there is 100 times more zinc in a pound of oysters than there is in a pound of milk I think if we search along the lines of nutrition here and think of the whole ch'ld, its growth sexual devel pment everything, we may come out with something that would be simple. If we lived naturally perhaps we shouldn t have all this trouble. I wonder if children in other countries have the acne we have in our American children. The European children do not.

Dr. Sulzberger I agree w th Dr Gerow that many links were left out of that chain. B t I did state that certain foods do produce outbreaks of acne in certa n individuals. In some few cases I have even seen milk do it. Chocolate is the most common of these foods. But the evidence that t s the general state of nutrition that lead to acne not good. It occurs in undernourished populations as well as overnourished ones. Although acne has a distribution that varies throughout the w rld and there is somewhat more acne in certain reas of the world than others, we cannot link these variations with the diet

Dr. Rothman Dr Gerow was your point that milk may be acnegenic or ice ersa?

Dr. Gerow I ha e seen ery severe case of acne in student

in my class who came to me afterwards. He said he had been to a dermatologist who said nothing could be done about it. I once read that potassium had something to do with fat metabolism. I suggested that the doctor give the student a prescription for five grains of potassium chloride a day and that he cut out the milk. Within two weeks he was cleared. So I believe that salt comes into the picture. There is sodium-potassium balance. Today you see people sprinkling the salt all over. Man in the past did not eat pure sodium chloride. We used to give our children sea salt. I still think that potassium linked up with a lot of other things, might have something to do with acne.

DR. BURTON: I was astonished to hear that a condition is called a disease which has an incidence of 99% in the adolescent ages and in 50% of the cases is serious. I wonder seriously whether or not we have a right to call this a disease. I think this should stir our thinking about this whole problem. After all, should we, since it causes such a dramatic emotional state, which is entirely due to our thinking about this problem—our social thinking, characterize it as a disease even when it is mild. Maybe we should do something in this direction. Maybe we should talk about people who are acne deficient. They are the abnormal. The 1% who are acne deficient are the ones we should worry about. Of course we should worry about the exacerbations and when it becomes most uncomfortable. We talk about the scarring. But it wasn't too long ago that the women put on beauty spots, which looked to me very much like these pictures of acne, when they went out for the evening. There are many Europeans who are very proud of the saber scars on their faces. We could do something in changing our attitude. But more seriously, I agree with the last speaker that there is something for which the stimulus is apparently the normal physiological changes of adolescence. It produces this discomfort. I do not believe that in the natural state, whatever that is, the physiological changes do lead to such discomfort. They certainly would not lead to this emotional trauma if we had the right attitude to this thing. I can't help feeling that we ought to look closely into the incidence in primitive tribes and so on and find out if this is really universal. I can't help feeling that there is some accompaniment of our civilization, the way the civilized people live, that is responsible. I don't know this, but I would like to ask Dr. Sulzberger if there have been any data produced on really primitive tribes. Maybe the factor is the use of soap. Maybe we shouldn't wash with soap. I remember during the war that there was a problem of prickly heat in the troops in the tropics and there was a very nice piece of work done by Ken O'Brien, an Australian, on the problem, a good scientific research in which he

concluded that prickly heat was brought on by the use of soap Maybe it is something else in the way we live. I m stirred up to say this because of hearing that here is a disease in which 99% of adolescents participate.

DR. SULZBERGER. The very high incidence does not mean that a manifestation is not a disease no matter how high its incidence. You realize that the incidence of tuberculosis formerly was 90% or more, judged by positive tuberculin tests in many cities. You realize that from 35% to 75% of all people will get poison ivy if they are exposed to it. So the high incidence does not mean that a thing is not a disease. There are diseases that affect almost 100% of the population. As far as the other aspects of what Dr Burton said, I have no information as to the occurrence of acne in primitive tribes. But it seems to me that there is a contradiction in what he said, because while the increased function of the p losebaceous apparatus at puberty is a physiologic happening and not a disease, when the hyperfunction leads to papules, pustules, scarring, and the disfigurement which I have shown, this is a disease What I tried to show in the pathogenetic acnegenic chain was that other potentially harmful things must be invol ed in various countries, but I don t know really what the factors are I have had acne patients that have gone from the U.S A. to England and have cleared up and have come back to the United States and got their acnes right back. These were older patients who didn t have the usual spontaneous cure. They were apparently liv ng the same sort of lives in England as in the U.S.A yet n England they cleared up I have been struck in looking at people in theatres and on the streets of London that acne is quite rare compared with what one sees in New York City on the street and in the theatres and other places. In France and Italy it is more common than in England. But I have the impression that the highest ncidence may be in New York.

DR. VAN SCOTT We have wondered about the role of chocolate which you specifically mentioned. A group of six teenage volunteers who had acne were purposely given six chocolate bars per day and an ointment of hocolate applied to half of the back of these indi iduals. O er a two-week period of t me we were unable to detect any increase in severity of the lesions generally or locally

DR. SULZBERGER. The incidence of exacerbations by chocolate is not as frequent as to be demonstrable in six patients taken at random. You m ght have to do the experiment on 600 times 6. There is no doubt that I have cases in wh ch I could repeatedly produce acne by feeding them hocolate nd have the a ne clear up under treatment and repeatedly produce it again. That cl nical observ tion is to my mind secure only I think the incidence of cne

caused to exacerbate by chocolate or any ingestant is not high I wouldn t expect you to produce it in six people chosen at random and fed chocolate.

DR. SUSKIND The age of susceptibility is a most interesting aspect of acne. We made two observations which relate to this problem in persons with chemically induced acne. In a group of 230 persons affected with chloracne of occupational origin the age range of those affected was 24 to 65 No apparent differences in severity could be correlated with age. We had no elderly persons in this group On the other hand, when we attempted to induce acne by local application of chemical acnegens we found that the skin of subjects in the 70- to 85-year age range was refractory to the stimulus. There appears to be even in acne provoked by local agents, a critical age beyond which the skin is apparently not responsive.

IV Pathogenetic Factors in Premalignant Conditions and Malignancies of the Skin

ETIOLOGIC FACTORS AND THE PATHOGENESIS OF PREMALIGNANT AND MALIGNANT LESIONS OF THE SKIN

RAYMOND R SUSKIND AND A. WESLEY HORTON

The Kettering Laboratory Department of Preventive Medicine and Industrial Health College of Medicine University of Cincinnati Cincinnati Ohio

There are two major sources of information regarding the etiologic factors in cancer of the skin. They are (*a*) clinical and epidemiologic information based on observations made upon man and (*b*) reproducible observations derived from controlled animal experiments.

It will be the objective of this review to examine some of the *available* evidence from both sources to provide perhaps, a better understanding of the susceptible cells, the nature of the provoking agents, and the mechanisms involved in the production of neoplastic lesions of the skin Since the clinical problems of man involve the epidermis chiefly we shall restrict our discussion to epidermal tumors.

We have chosen to discuss a few of the factors, the etiologic importance for which in man there is good support and also those for which there is reasonably good correlation between observations made on human beings and those on experimental animals.

Human Tumors

The premalignant and malignant lesions of human skin provoked by chemical or physical stimuli from a pathological view

point, are indistinguishable from senile keratoses, xeroderma pigmentosum basal cell epitheliomas squamous cell epitheliomas, and related pathological entities which arise in the general population

The counterparts in experimentally provoked tumors of the skin of mice and rats are the premalignant papillomas and keratoses, and the type of epithelioma which is similar histologically to the human squamous cell carcinoma.

It appears that a variety of biological physical and chemical factors has been studied experimentally in animals and has provided substantial support for the opinion that these factors are operative in human cancers of the skin Only a small fraction of the total number of human skin cancers which occur can be causally related to a specific physical or chemical agency The vast majority that are observed and treated by physicians are regarded as spontaneous for want of better information in the individual case An examination of epidemiologic data should, to some degree modify this attitude

Various factors biological physical and chemical may be enumerated with the warning that although there is considerable information about the significance of some of these there is little about others. The so-called biological factors are inherited susceptibility skin color sex specific sites, and age Of some importance also is the induction or latent period There may be immunologic considerations as well The important physical factors are mechanical trauma burns actinic radiation or ultraviolet light ionizing radiation from x ray sources, radium radioisotopes, and cosmic rays. Among the chemical factors which have been shown to cause precancerous and cancerous lesions of the human skin are materials contained in or derived from petroleum coal shale and compounds of arsenic

Heredity plays an obvious role in the grossly abnormal type of sensitivity of human skin to sunlight *for example in xeroderma pigmentosum* The precancerous and cancerous changes which develop in children affected by this disease are discussed in another paper In the realm of normal skin there is little information available concerning the anatomic and physiologic

factors which appear to influence epidermal susceptibility except for pigmentation. On the basis of some experimental work it appears that hormonal as well as immunologic factors may affect the epidermal response to carcinogenic agents.

It is well known that Negroes and other pigmented persons are less likely to develop skin cancer than Caucasians. Among

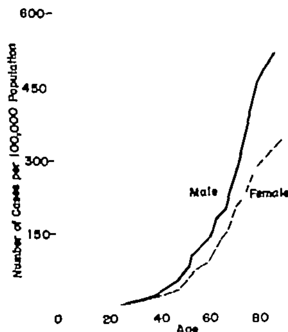


FIG. 1 Skin cancer incidence rates by sex and age (1)

the nonwhites (including Negroes) in the United States, the incidence of skin carcinoma is very low in comparison with the white population (1). The data from which we shall quote are from an excellent study conducted by the United States Public Health Service compiled and interpreted by Dorn and Cutler (1). They examined the rates of all cancer types in three geographical urban areas in the United States as follows

1. North: Chicago, Detroit, Pittsburgh and Philadelphia
2. West: San Francisco and Alameda County and Denver

3 South Birmingham Atlanta New Orleans, Dallas, and Ft Worth

The extremely low rate in the Negro is practically unaffected by the geographic area as well as by age (Table I and Fig 9)

TABLE I Cancer of the skin
Incidence rate per 100 000 population 1917 (1)

	Male		Female	
	Face head, neck	Other	Face, head, neck	Other
White				
North	96.8	6 6	90.5	4.9
South	*120 6*	*22.7*	*7?*	*15.8*
West	80 8	11.8	51 1	12.9
Non white				
North	2.1		0	2.9
South	2 5	2.0	1	4.3

This is not true of the white population A recent survey in Honolulu demonstrates that skin cancer is 45 times as common among Caucasians as among non-Caucasians (9) The figures in Table I demonstrate quite vividly also the influence of exposed site geographic location and to some degree sex.

Over 90 per cent of skin cancers are found on the exposed area of the face neck hands and forearms (Tables I and II)

TABLE II Cancer of the skin
Exposed and nonexposed sites 1917 (1)

Site	Males	Females
Face head neck	11 6	?9 1
Upper extremities	3 7	0
Trunk	3 1	9
Lower extremities	1 3	1 5
Unspecified site	*1.0*	*0 7*
Total	50 9	36

This is one of the most potent clues that sunlight itself is a major etiologic factor in the precancerous or cancerous process which cannot be attributed to a specific chemical or other physical agent

Blum (3) lists five reasons why sunlight can be regarded as a carcinogenic agent. Two of these reasons have already been mentioned. (*a*) most skin cancer occurs in exposed sites (*b*) pigmented persons (who are relatively immune to sunburn) do not develop skin cancer The other three are that (*c*) skin cancer occurs more frequently among outdoor workers (*d*) ultraviolet radiation of wavelengths present in sunlight induces cancer of

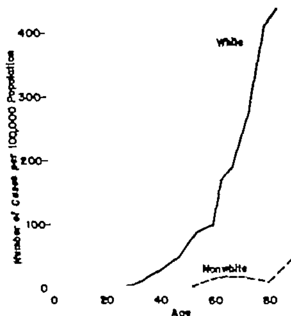


FIG. 2. Skin cancer incidence by race nd age 1917 (1)

the skin of mice and rats (*e*) cutaneous cancer is more common in the southern than in the northern latitudes.

In such states as Iowa, where more than half the population lives in rural areas and small towns, the incidence of skin cancer is 61 per 100 000 males and 35 per 100 000 females as compared with a corresponding rate of 33 and 5 males and females, respectively in American cities of the same latitude as Iowa The degree of exposure, therefore at any latitude is important.

It has been demonstrated experimentally that ultraviolet

wavelengths not longer than 3200 A and as short as 2537 A may induce tumors in the skin of mice and rats (3). This is essentially the same range of energy which produces sunburn in human skin.

An examination of cancer rates for all organs reveals that only in the case of skin cancer is there a clear-cut difference on the basis of geographic location, the rate being greater in the south than in the north (Table III). While the wavelengths that

TABLE III. Cancer of the skin
Age-adjusted incidence rates per 100,000 white population, 1947 (1)

	Males	Females
South	113	88
West	90	61
North	33	[illegible]

are presumably carcinogenic for man compose only a small fraction of total sunlight, this fraction changes considerably with latitude.

The over-all incidence of skin cancer is somewhat greater in the white male than in the white female (1) (Tables I–III). There are several possible reasons for this difference. The most plausible explanation is that the number of women engaged in outdoor work is considerably smaller than that of men and that the degree of exposure of women who spend time in the sun is not so great. In some instances the female use of cosmetics may reduce the penetration of ultraviolet rays.

As is true of other types of human cancer, those involving the skin are more likely to develop as the person grows older (Fig. 1). In the nonwhite person the increase in incidence with aging is very slight. New lines of evidence from both epidemiologic and experimental sources throw doubt on the venerable supposition that the aging process itself induces or predisposes the skin to the induction of cancer. One cannot discuss the age factor without considering the latent period or induction time. This is the period of time which elapses between the initial exposure to the carcinogenic stimulus and the appearance

of visible precancerous or cancerous lesions. In animal experiments, the induction time will vary with the type of carcinogenic stimulus, dosage accelerating or cocarcinogenic agents, synergistic agents, species of animals and many other factors. A *single* exposure to a carcinogenic agent is unlikely to result in neoplastic changes. This is especially true in the case of chemical carcinogenesis. In the field of occupational cancer there are numerous examples of variation in latent period, a subject which we shall discuss later. As one can see from the incidence curves, most human skin cancers are noted after the 40th year. Thus incidence curve rises sharply at age 60. The increase in incidence with advancing age may very well represent a long latent period involving carcinogenic stimuli of low potency or of intermittent or infrequent occurrence (4). The concept that ultraviolet radiation to which everyone is exposed to some degree (some more frequently and intensely as well as to more actively carcinogenic wavelengths, than others) is a major stimulus in human epidermal cancer has good support. The reason however that some persons develop cancer and others do not, may not be entirely related to the severity of their exposure to ultraviolet light; there are other intrinsic as well as extrinsic factors which must be considered. Resistance to the development of tumors, as has been demonstrated experimentally, may also involve genetic, hormonal, dietetic, immunologic and other metabolic factors, as well as external physical and chemical factors. In connection with immunologic considerations, we might even speculate that the immunologic resistance of human beings to the growth of neoplastic epidermal cells is inherited, or is acquired early in life, and that this resistance decreases with advancing age to the point where the neoplastic cells grow with less restriction.

Animal Observations and Correlation with Human Experience

Certain industrial materials derived from coal, petroleum and shale which are known to be carcinogenic for human skin have reproduced morphologically similar precancerous and can-

cerous lesions of the skin of animals, when applied thereon. The specific chemical structures of some but by no means all of the carcinogens in these complex industrial mixtures have been identified. Certain others have been classified but not identified as individual compounds. In 1921 a Swiss dermatologist, Bloch (5) recognized the component of coal tar as a cyclic *hydrocarbon which was concentrated in the high boiling fractions.* The first known pure chemical compound found to be carcinogenic for the skin of the mouse was dibenz(*a*,*h*)anthracene It was synthesized by Kennaway and Hieger (6) Since that time benzo[*a*]pyrene has been isolated from coal tar (7 8) and more recently from cracked petroleum mixtures (9) It has also been identified in atmospheric dust (10) shale oil (11) and automotive exhausts (12) Although there is no direct evidence that this compound will cause cancer of the human skin its carcinogenic effect on the skin of animals is well documented (13)

When a known polycyclic hydrocarbon or a complex mixture *from coal tar or petroleum containing a carcinogenic agent is* applied upon the skin of a mouse certain important variables must be dealt with adequately if satisfactory information regarding the carcinogenic potency of the material is to be obtained These include the concentration of carcinogen the total dose per application the schedule or number of the applications, the vehicle in which the carcinogen is applied and the state of health of the mouse (or mice) In the case of the petroleum or coal tar mixtures certain noncarcinogenic components of the mixture as we shall point out may influence the result significantly

These qualitative and quantitative relationships and perhaps others as well are of ultimate importance in human experience in understanding why in some occupations involving exposure to such industrial materials the occurrence of skin neoplasms is common while in others few or none occur In some instances, the time which may elapse before precancerous or cancerous lesions are noted may be relatively short and in others, long At this point the data of Henry (14) who conducted a survey of several thousand cases of cutaneous cancer

among British workmen who had handled products of coal tar shale or mineral oil should be reexamined

The majority of cases among men who handled pitch and tar occurred within 20–24 years after commencing work, but most of those associated with the handling of shale and mineral oil occurred within 50–54 years. Hence it appears that pitch and tar are capable of producing disease in man more quickly than mineral oil. It should be noted too, that scrotal cancers can be regarded almost exclusively to be of occupational origin Those which occur on exposed sites such as the hands or face, may be under suitable circumstances, suspected as being occupational in origin but other nonoccupational stimuli must also be considered.

It is appropriate to examine our experimental data to see if they can provide some explanation of the differences referred to above. It is almost axiomatic in chemical research that, in order to learn the mechanism of a reaction one must determine the manner in which the rate of the reaction varies with the changes in the initial concentration of the reactants An analogous approach to the mechanism by which certain oils produce precancerous lesions and carcinoma, when applied repeatedly upon the skin of mice has proved fruitful It seems likely that more may be learned about the mechanism of carcinogenesis by investigating the rate at which tumors can be induced in animals under various experimental conditions, than by determining only the incidence From the standpoint of pathogenesis we must be concerned with quantitating the induction period since it is during this period that the cellular changes occur and the potentially neoplastic or malignant cell is produced and stimulated to grow

It has been found that the dose of a carcinogen applied in an appropriate vehicle may be expressed most usefully in the unit of weight per unit of area of the skin per week (15) By this stratagem the rate of induction of tumors by such polycyclic hydrocarbons as benzo[a]pyrene and 3-methylcholanthrene in a variety of common solvents, may be equated (Fig 3) The intrinsic capacities of the different solutions to spread

upon the surface of the skin vary considerably and the total quantity of the polycyclic hydrocarbon required to obtain a given dose per unit area will vary accordingly Solutions for which this characteristic relationship between dosage and rate

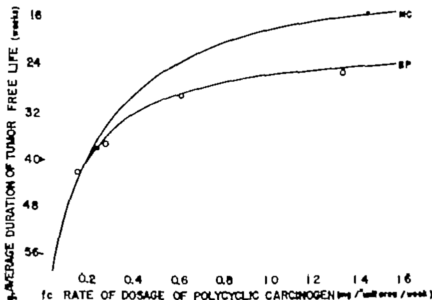


FIG. 3 The rate of induction of papillomas in C3H mice by repeated application of 3-methylcholanthrene (MC) and benzo[a]pyrene (BP) in nonaccelerating solvents. The unit area is the area covered by 100 mg of solution having a relative spread of one

Equation for benzopyrene

$$c_m = \frac{0}{fc + 0\,1} + 90$$

Equation for methylcholanthrene

$$= \frac{13}{f \; + 0} +$$

of carcinogenesis holds are classified as nonaccelerating for reasons which will be apparent subsequently Some of the solvents which have nonaccelerating characteristics are benzene n-octane decalin and white mineral oil of high viscosity These are used frequently in experimental work on cancer of the skin

In contrast, certain less common solvents such as *t*-dodecylbenzene, *n*-dodecane and diamylnaphthalene accelerate the carcinogenic action of benzo[*a*]pyrene and methylcholanthrene, even though these solvents when highly purified are noncarcinogenic (16) The effects of benzene and dodecylbenzene are compared in Fig 4

When a low concentration e.g 0 002 per cent, of a strong carcinogen is applied in a nonaccelerating medium more time

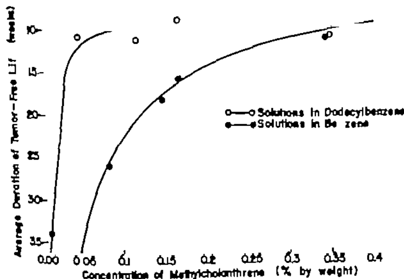


FIG. 4 Relative rates of induction of tumors by solutions of methylcholanthrene in benzene and dodecylbenzene in tests involving three 100-mg applications each week.

than the life span of a mouse would be required for the induction of tumors. Hence tumors are not observed in such an experiment. When the solvent is an accelerator however this very low concentration is adequate to induce tumors in all the mice. Moreover certain polycyclic hydrocarbons which are generally considered to be essentially noncarcinogenic, such as benz(a)anthracene have been found to be capable of inducing tumors in all the mice if applied as a solution in a suitable accelerating medium.

What is the significance of these findings in terms of cancer of the human skin? Let us compare such experimental data with the clinical information obtained in relation to certain types of occupational cancer (Table IV).

The latent period of skin cancer among workmen who handle pitch is relatively short, as is the case among paraffin wax pressmen in shale oil and mineral oil refineries. It is to be noted, however, that this similarity in latent period is associated with exposure to materials of quite different composition, as is shown

TABLE IV

Material	Relative carcinogen content	Probable percentage of long-chain accelerators	Mice, average latent period* (weeks)	Human, average latent period (years)
Paraffin distillate (slack wax)	Low	High	[illegible]0–3[illegible]	[illegible]0 or more
Spindle oil	Low	Low to moderate	60	40–50 (Henry)
Coal tar	High	Negligible	1[illegible]–27	[illegible]3 (Henry)
Pitch	Very high	Negligible	—	[illegible]3 (Henry)
White mineral oil	None	Low	Noncarcinogenic	Noncarcinogenic

* Three applications per week.

in Table IV. In coal tar and pitch the concentration of carcinogen is high, while the concentration of long-chain accelerators is negligible. On the other hand, the concentration of carcinogen in the wax distillate is low and the concentration of long-chain accelerators often high. There appears to be considerable variation among distillates with respect to their content of accelerators. This may explain in some measure the variable incidence of cancer of the skin among wax pressmen in different refineries, including its nonoccurrence in many. Among persons who come in contact with spindle oils, such as mule spinners in the British textile factories, the severity of exposure in terms of the carcinogenic content of the oils is quite low. The concentration of long-chain accelerators in such oils is less, usually

than that in wax distillates. While a large number of skin cancers among mule spinners has been reported their average latent period is relatively long When materials of the type indicated above are applied upon the skin of mice, under appropriate experimental conditions the responses of the mice correlate with those indicated above in men to such an extent as hardly to be fortuitous (Table IV)

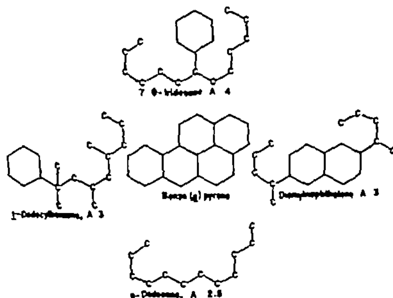


FIG. 5 Carbon skeletons of several typical carcinogens and accelerators. The numerical values indicate relative accelerating activity of each solvent using benzene with value of 1.0 as a standard.

One cannot discuss these problems without mentioning the tremendous influence of hygienic factors. There is ample clinical and experimental evidence to demonstrate that the proper cleansing of the skin will decrease the rate of tumor formation and lengthen, significantly the time of induction of tumors.

Structural similarities between typical carcinogens and accelerators are shown by the carbon skeletons in Fig 5 (16) The relative accelerating activity of each solvent using benzene with

an accelerating activity of 1 0 as the standard, is indicated. The freely rotating alkyl chain is apparently an essential characteristic of the accelerator If the alkyl chain which is characteristic of all these compounds, is longer than a critical length the compound ceases to be an accelerator A compound which represents the completely cyclized version of diamylnaphthalene has no accelerating activity It has been reported too that hydrogenated derivatives of the five ringed carcinogens are inhibitors (1/) of the induction of carcinomas.

It has been noted above that, when the solvent is nonaccelerating the rate of induction of tumors by a benzo[a]pyrene solution is a function of the *concentration* of the carcinogen in the solution and the number of applications each week (yielding a certain dosage per unit area per week) It is not influenced by variations in the total quantity of solution used for each application as long as the same part of the back of the mouse is exposed every time For example the application of 50 mg of solution covers roughly twice the area covered by 25 mg yielding essentially the same dose of carcinogen per unit area in either case and the same rate of induction of tumors

In contrast when accelerators are added to the solution in significant concentration (> 90 per cent) the quantity of solution used for each application becomes a most important variable The rate of induction of tumors may be accelerated strongly when 50 mg of solution is applied each time and yet not significantly changed when 10 mg is applied (depending of course on the actual concentrations and activity of the particular accelerator employed) It is also noteworthy that 90 mg of pure accelerator is very much more effective than 100 mg of a mixture containing 90 per cent of the accelerator and 80 per cent of nonaccelerators.

The results of investigations of the rate of induction of tumors by solutions containing so little carcinogen that only about 9 per cent of the mice develop tumors may be particularly helpful toward an understanding of the difference in the roles of the carcinogen and the accelerators When the solvent is nonaccelerating most of the tumors appear late in the life of the mice. The total incidence of the induced cancer seems to have

been limited primarily by the death of the animals and by the slow growth of the neoplasms to detectable size rather than by any failure of the carcinogen to produce its effect on all of the mice.

Again in contrast when the medium is strongly accelerating in order to produce tumors in 25 per cent of the mice only about one-tenth of the concentration of the carcinogen is required. However most of the tumors thus produced appear after a relatively short latent period (in about 15–20 weeks after the first application in experiments involving three applications each week) Here it appears that the incidence is definitely limited by the availability of the carcinogen but, at the same time that the carcinogenic reaction in the susceptible mice takes place very early in the series of applications. The similarity in the latent periods for the few tumors produced, as well as their relative shortness, suggests that the role of the accelerator is to facilitate the growth of a cell or group of cells. These cells have been rendered potentially neoplastic by the carcinogen which in the absence of an accelerator would not have acted so promptly We speculate that the accelerator may enhance the absorption of the carcinogen into the susceptible cell The possibility that some naturally occurring immune mechanism may be exerting a cancerostatic action and that the role of the accelerator is to inactivate such an immune system is under investigation currently It is possible that the same system may be involved in the natural resistance to infection since it has been noted (15) that mice exposed to accelerators appear to be much more susceptible to infection than are the controls. The possibility that the accelerator may inhibit a metabolic change whereby the carcinogenic agent becomes noncarcinogenic must also be considered.

It has also been found that when the accelerator (without the carcinogen) is applied upon the skin prior to or following the application of a carcinogen dissolved in a nonaccelerator carcinogenic activity is enhanced. The effect of preconditioning mouse skin with *l*-dodecylbenzene and ~ phenyldecane is quite striking (Table V) It was apparent that mice were rendered much more susceptible to the carcinogenic action of a catalyti

cally cracked oil by a prior application of accelerators upon the skin Not only was the latent period reduced considerably in the preconditioned mice, but the incidence of tumors increased. The presence of a small and normally ineffective amount of

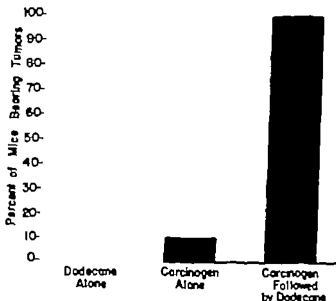


Fig. 6 Incidence of tumors following a single application of a strong carcinogen as contrasted to incidence rates when an accelerating solvent, dodecane was applied subsequently

accelerators (indicated by other tests) in Oil No 9 (Table V) was also an important factor in this demonstration of a preconditioning of mice by accelerators.

It appears that acceleration of carcinogenesis by long chain compounds may be analogous to the "cocarcinogenic" action of croton oil described by Berenblum (18) *It is demonstrated in the bar graph of Fig 6 that the incidence of tumors following* a single application of a strong carcinogen (7 12-dimethylbenz(a)-anthracene) may be raised from a very low value to essentially 100 per cent by the subsequent application of an accelerating

TABLE V Preconditioning of C3H mice to carcinogenesis

Materials applied upon skin of mice during: First 6 weeks	Seventh week to end	Effective number of mice	Number of tumor bearing mice	Average duration of tumor free life, t (weeks)
Oil No. 9 (cat. cracked)	Oil No 9	9	9	36.2 ± 4.5
Dodecylbenzene	Oil N 9	34	34	15 7 ± 2.3
2-Phenyldodecane	Oil No. 9	17	16	15 4 ± 2.2

hydrocarbon. The latent period was again about 15 weeks (when the accelerator was applied three times each week)

It seems probable that the basic change or mutation occurred in the skin of all the mice within a few days after the application of the carcinogen. The abnormal cells, thus produced in relatively few instances, multiplied to produce a neoplastic tissue of visible size without further stimulation. Accelerators produce a condition in the animal which makes it possible for this growth to take place almost universally The rate of growth has been found to be directly proportional to the frequency of application of the accelerator

Summary

Significant etiologic factors in spontaneous cutaneous cancer have been discussed. The intensity of intermittent exposure to ultraviolet wavelengths which produce sunburn and the inherent susceptibility of the epidermis are probably the major factors responsible for skin cancer of nonoccupational origin

Relationships between the essential variables which affect the potency of some experimental carcinogens have been presented. Insight regarding etiology and pathogenesis may be gained by studying the enhancing effect of certain long-chain aliphatic and related hydrocarbons which may be regarded as accelerators (1) Solutions of carcinogenic compounds in accelerators induce tumors in the skin of mice at a much higher rate than

do solutions in hydrocarbon solvents of lower molecular weight (2) The accelerating solvents are capable of preconditioning the skin of the mouse so that it is more responsive to subsequent applications of a carcinogenic material particularly if the latter already contains a small amount of the accelerating component (3) The accelerators, like croton oil appear to promote carcinogenesis initiated by a single application of a carcinogenic hydrocarbon Some speculative considerations regarding the mode of action of accelerators are presented.

The different rates of tumor formation observed among workmen who come in contact with various industrial materials such as coal tar and certain fractions of shale and mineral oil appear to lend themselves to explanation in terms of the relative concentrations of carcinogens and accelerators in these materials The clinical data as regards the rate of tumor formation are paralleled closely by experimental observations on mice subjected to contact of their skin with comparable industrial mixtures The close correlation between epidemiologic findings and experimental data and the significant information derived from this comparative investigation justify the continued use of animal experimentation as a means of studying the etiology and pathogenesis of cancer of the human skin

REFERENCES

1 Dorn H F and Cutler S. J *Morbidity from Cancer in the United States* Public Health Monograph No 29 19

2 Allison S D and Wong K L Skin cancer *A M A Arch Dermatol* 76 73 739 (19)

3 Blum H F Sunlight as a causal factor in cancer of the skin of man *J Natl Cancer Inst* 9 17 38 (1948)

4 Kennaway E L and Kennaway N M *The relation between the incidence and incubation period of cancer in man* *J Brit Med J* 159 161 (1911).

5 Bloch B and Dreifuss W Ueber die experimentelle Erzeugung von *Carcinomen mit Lymphdrüsen und Lungenmetastasen* durch Teerbestandteile *Schweiz med Wchnschr* 51 103 105 (1921).

6 Kennaway E L and Hieger I Carcinogenic substances and their fluorescence spectra *Brit Med J* 1 1044 1046 (1930)

7. Hieger I. Isolation of a cancer producing hydrocarbon from coal tar I. Concentration of the active substance *J Chem Soc 1933* 395-396
8. Cook, J W Hewett, C. L., and Hieger I. Isolation of a cancer producing hydrocarbon from coal tar II. Isolation of 1,2 and 4,5-benzopyrenes, perylene, and 1,2-benzanthracene. *J Chem. Soc., 1933* 396-398.
9 Tye, R Graf M J., and Horton, A. W Determination of benzo[*a*]pyrene in complex mixtures. *Anal. Chem* 27 248-253 (1955)
10 Waller R. E. The benzpyrene content of town air *Brit J Cancer* 6 8-21 (1952)
11 Berenblum, I and Schoental, R Carcinogenic constituents of shale oil. *Brit J Exptl. Pathol.* 24 232 239 (1943)
12. Kotin P Falk, H L., and Thomas, M Aromatic hydrocarbons II Presence in the particulate phase of gasoline-engine exhausts and the carcinogenicity of exhaust extracts. *Arch Ind Hyg. Occupational Med* 9 164 177 (1954)
13 Hartwell, J L. Survey of compounds which have been tested for carcinogenic activity *U.S Publ c Health Serv Publ No 149* 1951
14 Henry S. A Occupational cutaneous cancer attributable to certain chemicals in industry *Brit Med Bull* 4 389-401 (1947).
15 Horton, A. W and Denman D T Carcinogenesis of the skin A re-examination of methods for the quantitati e measurement of the potencies of complex materials *Cancer Research* 15 701 709 (1955)
16 Horton, A. W Denman D T and Trosset, R P Carcinogenesis of the skin. II The accelerating properties of aliphatic and related hydrocarbons *Cancer Research* 17 758-766 (1957).
17 Kotin P Falk H L., Lijinsky W and Zechmeister L. Inhibition of the effect of some carcinogens by their partially hydrogenated derivati es. *Scien e* 123 102 (1956).
18 Berenbl m, I and Shubik, P The role of roton oil applications, associated with a ingle pa nt g of a carcinogen, n tumor induction of the mouse s skin *Brit J C ncer* 1 379-38 (1947).

Discussion

Dr. Rothman I would like to ask two questions. The first one refers to the ac lerators I wonder whether they ha e ny l n cally

noticeable irritating effect. If not, it is hard to understand the positive results of experiments in which first the accelerator was given and the carcinogen was applied afterwards. If the accelerators promote the subsequent absorption of carcinogens they must burst cell membranes in the epidermis, as it was emphasized yesterday and I hardly can imagine that such damage can be done without obtaining subsequent inflammatory reaction.

My second question refers to the carcinogenic action spectrum of ultraviolet radiation in mice. I can t recall that H Blum has actually demonstrated carcinogenic action of the wavelength 2537 A. If he did this is somewhat in contrast to our own experimental work which Dr Lorincz will discuss. The 2537 A line of the mercury arc does not cause true sunburn It causes a short lasting erythema (pure vasodilatation without inflammation) and it does not leave pigmentation To my knowledge carcinogenic effect is restricted to the sunburn range in the narrower sense which is indeed a narrow range extending from 2900 to 3100 A

DR. SUSKIND Most of the long-chain accelerators are primary irritants and produce inflammatory changes in the dermis and epidermis but when pure they are not carcinogenic

In connection with the carcinogenicity of radiation as short as 2537 A, Blum has produced skin cancers in mice with a mercury arc source at a very low pressure in which almost all the radiation emitted was in the 2537 A line. Such energy levels are of no importance in the human exposure to sunlight since 2900 A is the shortest wave length reaching the skin in appreciable amounts from solar sources

DR. LORINCZ We carried out a few experiments a number of years ago which we never published. We tried to protect mice against the carcinogenic effect of ultraviolet light by application of a *p*-aminobenzoic acid sunscreen in propylene glycol solution *p*-Aminobenzo acid absorbs the sunburn rays around 3000 A but n t the 2537 A line of the mercury arc. We found that this screen wa effecti e in om pletely preventing ultraviolet induced carcinoma Our ligl t sour e was a therapeutic hot mercury quartz lamp

DR. ROTHMAN The protection of the mouse e rs wa indeed com plete When we went on with the rad ation the mice developed car inomas on their tails, these rea being also rel tively free f hair If both ears and tails were p r tected, carcinom developed n

H F Blum and S W Lipp ncott Carcinogenic effect enes f ult violet radiation of w length 2537 A *J N tl C cer I st* 3 11 16 (1942).

H. F Blum Su light as causal factor in cancer of the sk of man *J N tl. Ca cer I st* 9 17 18 (1948).

the eyelids. Thus *p*-aminobenzoic acid was absolutely protective although it does not protect against the 2537 A line.

DR. HORTON In regard to your first question, Dr Rothman all the known accelerating hydrocarbons are definitely primary irritants. However a number of the nonaccelerators seem to give the same primary irritation I don t believe Dr Suskind intended to infer that the only possible mechanism whereby accelerators work is by increasing the permeability of the epidermis to carcinogens. We have reasons to suspect a systemic influence of the accelerators since they make the animals much more susceptible to certain types of infection. Thus the mechanism may be much more complex than a simple local effect.

DR. LORINCZ. The observations on the influence of the accelerators are very interest ng, particularly the experiment in which a single carcinogen dose was applied and was followed by subsequent applications of accelerator to produce a very h gh incidence of neoplasms. To me this would suggest that these accelerators somehow interfere with the imm une mechanism of the host. One might conceive that at the individual cell level potential carcinomas of the skin probably arise in very large numbers but that these cancerous mutant cells, generally differ sufficiently in antigenic makeup from normal cells to arouse immune reactions which take care of these incipient individual cellular neoplasms. If one then interferes with this immune mechanism by depressing antibody formation or delayed type reactivity the potential cellular cancers can proliferate freely to form gross tumors. I wonder f these accelerator compounds affect delayed type tuberculin sens ti ity or sensitization.

DR. SULZBERGER In reference to what Dr Horton and Dr Lorincz have just said, I am sure you recall the experiments of Drs. Herrmann nd Sherw n in which the adm nistration of cortisone in specified doses in a part cular range, just before and during the application of methyl holanthrene to carcinoma-susceptible mice, accelerated the rate of formation of the carcinomas substantially That might be an analogy to what has happened here, if you postulate that this i a systemic effect and has something to do with resistance to cause carcinogenesi system cally However I don t quite nderstand whether you postulate a sy temic effect of the accelerator Must you pply the carcinogen to the same area to which you ha e applied or are going to apj ly the accelerating solution or will the accelerator act f om distance? In other words, do you obta n cceleration if you pply the ccelerator to one site and the carcinogen to distant ter

DR. SUSKIND In answer to Dr Lorincz question bout the role of the cceler tor when employed fter a ingle dose of a carcinogen

this is a phenomenon which has been described some time ag). As you all know croton resin or oil was described by Berenblum as having just such properties. He speculated that there were two stages to carcinogenesis (*a*) an initiating phase in which the neoplastic or preneoplastic cell was formed (*b*) the promoting phase in which the cell grew either as a result of the continued exposure to the carcinogen or to some other agent which was not carcinogenic. When a solution of croton resin is applied after a single dose of dimethylbenzanthracene many more tumors are produced that would arise without such promoting treatment. Berenblum proposed that the action of the accelerator (he used the term cocarcinogen") was a promoting action which causes proliferation of the preneoplastic cell which one sees in the papilloma or the neoplastic cell which one observes in the squamous cell carcinoma However this does not explain several other observations made by Dr Horton and his group They observed an accelerating or enhancing effect when the skin was pretreated with the solvent and the carcinogen subsequently applied. Perhaps our solvents are of a different order of ompound than croton resin Dr Horton doesn t think so When the skin is either pretreated with the sol ent or when it is used as a solvent for the applied carcinogen ncre sed rate of tumor formation is noted. Dr Horton and his group are now probing into the pos il le mechanisms of action of the accelerator sol ents.

In answer to Dr Sulzberger s question regarding the application of the accelerating solvent to the same site or one remote from the application of the carcinogen in all the experiments to date the accelerating solvent and carcinogen ha e been applied to the same general area. We are in the proces of determining whether the en*hancing effect may be produced if the a celerator i applied to one* area nd the c rcinogen to another

QUESTION I would like to ask Dr Siskind or anyone else here if there is any indication that these agents have an effect on the mut tion rate of animal or human ells. We know that in microorganisms, dibenzanthracene nd *benzpyrene will accelerate the n utat on* rate

DR. HORTON We ha e no experimental evidence in direct a nswer to your question. In this mechanism we re presuming that the r inogen may have it ba ic response because it produ es a n utat on and that this actu lly may occur relatively early in th course of experiment that invol es any ignificant concent tion of a st ong carc nogen Whatever the accelerator does is just imply some al phase of the nechanism. Perhaps as someone uggested her inherent immune response is dep ressed by the ac eler tor th s pe mitt ng the abnormal ell to thr ve in an en ironment wh h other wise would hold it in heck

CLINICAL, HISTOLOGIC AND DIFFERENTIAL CONSIDERATIONS*

HERMANN PINKUS

Departments of Dermatology Wayne State University College of Medicine and Receiving Hospital and the Detroit Institute of Cancer Research Detroit, Michigan

The critical assessment of the development of concepts and an attempt at some kind of synthesis of modern views based not only on work in the field of dermatohistopathology but drawing also on advances in other branches of science such as general pathology anatomy and cancer research appear to provide the best approach to this topic. A cataloguing and technical description of the various tumors is unnecessary since the publication of Lund's (22) fascicle "Tumors of the Skin" which provides an excellent catalog and description of premalignant and malignant lesions of the skin. This discussion therefore will be confined to considerations, derived from the study of literature of normal skin, and of several thousand biopsies, and will be based on personal convictions. It will be controversial in some respects.

Interest in the clinical and histologic differentiation of skin cancer became lively around the turn of the century. A historical review therefore has to go back about sixty years. During this time an immense amount of facts, thoughts, and theories have been laid down in the literature. It is very difficult, if not impossible to contribute anything original to the concepts about skin cancer and if explicit credit is not given to prede

*Supported in part by research grant C 9072 from the National Institutes of Health, United States Public Health Service, and by research contract DA 49 007 MD 581 from the Research and Development Division, Office of the Surgeon General Department of the Army

cessors who proposed or opposed the views expressed the omission is not in malice, but solely to save time and present the involved subject as clearly as possible

Clinical Considerations

Considering clinical matters, one might point out racial differences in incidence and distribution of skin cancer as a subject of fairly recent investigation There seems to be a relatively greater susceptibility of light complexioned individuals not only to carcinomas of actinic origin but also to melanomas (27,33) On the other hand melanoma is relatively rare in Japanese and especially in Negroes (23)

Another point that is of more general interest to the practicing physician in this country is that in my experience there has been a considerable shift in the case material one sees in office practice It has become relatively rare although by no means unknown, to see large far advanced or neglected cases of carcinoma sarcoma or lymphoma Increased awareness of the lay public improved diagnosis and more effective treatment have had a greater impact in the field of cutaneous cancer than perhaps in any other specialty Many patients seek the doctor's advice for tiny and often insignificant lesions, and it has become a common task to reassure the patient and to combat cancerophobia.

No doubt many skin cancers are discovered at an earlier stage Figure 1 seems to bear this out. The data are taken from my biopsy material of basal cell epitheliomas for the years 1956/57 and ten years earlier 1946–47 Although the peak in both periods is in the seventh decade the percentage distribution indicates a noticeable shift to the younger age groups. The curve shows this more clearly than the relatively small drop in mean age from 62 to 58 years. As it is unlikely that people develop basal cell epitheliomas at an earlier age today than they did ten years ago these figures indicate that patients see their doctor earlier and that doctors diagnose many earlier lesions This impression is further supported by the fact that many of these

biopsies came from tiny papular lesions, often without ulceration and not more than a few millimeters in diameter

The shift in clinical material to younger smaller and therefore less characteristic lesions is noticeable not only in basal cell and squamous cell carcinomas, but also perhaps even more so in the lymphomas, especially mycosis fungoides and in the sarcomas, especially Kaposi's hemorrhagic pigmented variety The tumors and even the plaques of mycosis fungoides often are preceded for many years by innocent looking eruptions of

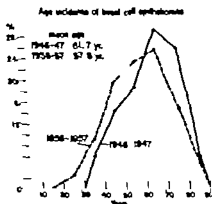


FIG. 1 Age incidence of basal cell epitheliomas encountered in biopsy material between August 21 1946 and August 20 1947 (solid curve) and between August 21 1956 and August 20 1957 (dotted curve). Based on 457 specimens.

the parapsoriasis type The infiltrating and ulcerating tumors of Kaposi s disease are preceded by stages in which the clinical and even the histologic differentiation from simple stasis dermatitis may be very difficult. The pathologist rendering a diagnosis of mycosis fungoides or Kaposi sarcoma may be taken to task several years later if the patient continues in good health However it is the clinician rather than the pathologist who must change his outlook Early lesions of Kaposi sarcoma may involute spontaneously new lesions may keep developing and disappearing for years. Mycosis fungoides may remain in the prefungoid stage for twenty years or more in exceptional cases

lesions may come and go with little or no treatment. In these premalignant stages in which the body manifests its ability to keep the disease in check it seems warranted to withhold the more severe forms of modern therapy which may be more destructive to the host's ability to resist than to the malignant process

In this situation the clinician's responsibility is to maintain a high level of suspicion without becoming an alarmist. He must practice the art of exact dermatologic diagnosis by close scrutiny and mental analysis of minute detail an art in which the pioneers of our specialty excelled To know a basal cell epithelioma from a squamous cell carcinoma a seborrheic keratosis from a senile keratosis, a melanoma from a black seborrheic keratosis or a thrombosed hemangioma an amelanotic melanoma from a granuloma pyogenicum these and other differentiations require a trained eye and a trained mind that can be acquired only by daily application over a number of years. *Their possession more than anything else is the distinguishing* mark of the dermatologist

Biopsy and histopathologic examination of course should not be neglected On the contrary any lesion that is considered worth removing certainly deserves microscopic examination The reasons for this statement range from the sporting interest of the clinician in having his judgment confirmed to reassurance of the patient and to medico-legal considerations. From the point of view of the histopathologist it is much more enjoyable to give an opinion to the clinician who submitted a considered differential diagnosis than to one who calls all his surgical trophies cysts moles, and tumors.

Histopathologic Considerations

Exact histopathologic classification of tumors may *be practiced* for two main reasons to satisfy the scientific spirit of the pathologist and for the practical purpose of prognostication The clinician wants to know from the pathologist how the tumor may be expected to react to various modalities of therapy and

what its biologic behavior may be in terms of local growth rate and metastasis. The pathologist's ability to deduce prognosis from microscopic examination of a tumor is based in part on objective criteria. Often, however, he follows conceptual rules of interpretation that may be derived from entirely different fields of research. Changes in concept may affect his judgment considerably. Therefore a few topics in which recent developments have led to major shifts of concept have been selected, foremost of which is carcinoma of the skin.

Carcinoma of Skin

Around the turn of the century it became established that there are two quite different types of skin cancer. In addition to the relatively fast acting, metastasizing, and eventually fatal type of tumor that we now call squamous cell carcinoma, there was found to be a more innocent, slowly progressive, and only locally destructive cancer to which Jacob in England gave the name "rodent ulcer." The most commonly accepted name for this second type of cancer is that bestowed by Krompecher of Budapest, "basal cell carcinoma" (17). The opinions regarding Krompecher's contribution to the field have varied from enthusiastic support to the biting comment of Lacassagne (11) that Krompecher contributed nothing but an inept designation. My personal opinion is that Krompecher contributed a great deal by establishing the unity of a variety of cutaneous tumors, many of which had been diagnosed as endotheliomas before him, and by setting forth diagnostic criteria. On the other hand, I feel that the designation he used in his first paper, "adenoid carcinoma of the surface epithelium" (16), is more correct than his later choice of "basal cell carcinoma," which indeed has given rise to much misunderstanding and futile argument and speculation. Many French and some English authors never took too kindly to Krompecher's view that this cancer originates in the basal cells of the stratified epithelium, but discussed its derivation from one or the other of the cutaneous adnexa, namely hair follicles or glands.

A new chapter and a period of comparative agreement was opened in 1922 by Darier and Ferrand (7,8) who gave a straight forward and clear classification of skin cancer on the basis of strict histopathologic criteria. They found that a certain per centage of carcinomas consisted almost exclusively of large prickle cells, others almost exclusively of small cells resembling basal cells, and still others of a mixture of both or of cu boidal cells of intermediate character They proposed a classifi cation in three groups typical carcinomas reproducing the keratinizing propensities of the epidermis, atypical carcinomas without this tendency and metatypical carcinomas, which might be either of mixed baso-squamous or of intermediate cell type.

They pointed out that this classification on histologic basis had great practical significance Prickle or squamous cell car cinomas required a much higher dose of x ray therapy than that thought sufficient for basal cell carcinomas. Inasmuch as 15-20% of all carcinomas were found to be of metatypical type that is, contained a squamous element that could be recognized only under the microscope histopathologic examination became of paramount importance in order to select the correct dose of x ray therapy Darier s findings and interpretation were soon corroborated by H Montgomery (96) in this country and Juon (14) of Jadassohn s school in Germany (Table I)

TABLE I Standard classification of epithelial tumors

Benign	Malignant
Adnexal	Basal cell carcinoma
	Baso-squamous carcinoma
Epidermal	Squamous cell carcinoma

This development with its simplicity and clarity was very satisfactory to all concerned to the pathologist because it gave him objective criteria for diagnosis to the clinician because it gave him definite principles of therapy and to the patient who was apt to receive more adequate treatment Darier s concept still is accepted by most

Only a few minds of speculative bend remained restive. They argued that everywhere in cancer biology there is a rule that the less differentiated the tumor the more aggressive and malig nant its behavior and contrariwise the more highly differenti ated a lesion the slower and less serious its nature Here in skin cancer the least differentiated type the atypical basal cell carcinoma, was a relatively harmless growth, slow in development and hardly if ever metastasizing [for details see Pinkus (29)]

Concept of Adnexal Tumors

This is a real dilemma. Its solution was sought by going back to older concepts. Lever (19,20) especially called renewed attention to the fact that many basal cell carcinomas show evidence of organization in the direction of adnexal structures hair hair sheath, sebaceous gland, or sweat gland. Sometimes it is not easy to say on microscopic examination whether a tumor should be classified as a benign cystic epithelioma, trichoepithelioma, or hidradenoma, or as a basal cell carcinoma Lever therefore pre ferred the name basal cell epithelioma and revived the con cept that basal cell epithelioma is closely related to benign adnexal tumors, generally considered to be of nevoid or hamar tomatous character He concluded that all these tumors, including basal cell epithelioma, are derived from the primary epi thelial germ an embryonic anlage that normally develops into the pilary complex consisting of hair follicle, sebaceous gland and apocrine gland. Squamous cell carcinoma, on the other hand, originates in the epidermis in consequence of various carcinogenic stimuli in post-fetal life.

Thus, according to this concept, we have two entirely differ ent types of carcinoma in the skin originating in different parts of the epithelial system and by different mechanisms There are no transitions between the two types. If prickle cells and keratin oc ur in basal cell epithelioma, they are evidence of rudimentary adnexal differentiation not evidence of epidermoid squamous ell car inoma. In a few instances squamous cell carcinoma may

develop secondarily in the epidermis above a basal cell tumor In support of this concept it can be said that highly undifferentiated and nonkeratinizing squamous cell carcinoma is quite different histologically and biologically from basal cell epithelioma

Lever postulated *persistence of adnexal embryonic rests into* adult life from which according to Cohnheim s theory benign tumors as well as basal cell epitheliomas could develop The latter are not truly malignant as they lack the power of metastasis. Thus squamous cell carcinoma remains as the only true carcinoma of the skin with the exception of rare adenocarcinomas derived from adult cutaneous glands.

Critique of Lever s Concept

Before this concept could take firm hold its two premises were challenged It was shown that neither the mechanism of pathogenesis nor the sources of derivation of basal cell and squamous cell tumors were rigidly different

Instances were quoted showing that basal cell epitheliomas could be induced by actinic energy be it sunlight or artificial ionizing radiation One of the examples is xeroderma pigmentosum in which the skin is overly sensitive to light Basal cell epitheliomas frequently are associated with squamous cell carcinomas and malignant melanomas in these patients. *Anderson* and Anderson (9) reported 11 cases of basal cell epithelioma in old x ray dermatitis and collected others from the literature Similarly in animal experiments tumors very much resembling basal cell epitheliomas can be produced by certain carcinogens notably by anthramin in rat skin

The hypothesis of embryonic rests is hard to maintain in the field of skin pathology In the last analysis an embryonic rest might be not *more than one undifferentiated cell still capable* of forming any of the adnexal structures. *Inasmuch as these* originate in fetal life from the basal layer of the epidermis, the seat of such a cell if it exists should be in the basal *layer of* the adult epidermis or possibly in the regenerative layer of some part of the pilary complex It would have t remain dormant

for several decades amidst continuously changing and proliferating neighbors. Moreover a cell of this type should be determined definitely as an adnexal germ and should not be capable of forming keratinizing epidermis.

Pluripotentiality and Equipotentiality

Within the last few years, however a considerable body of evidence has developed showing that all the matrix cells of the adult skin retain a high degree of pluripotentiality and probably are more or less equipotential. This concept was discussed in a paper read to the American Medical Association in 1952 (99) Much of the evidence comes from quasi-experimental experiences in wound healing. If all the epidermis is lost, as in a burn or in the donor site of a split skin graft, or more convincing still in a sanding or planning operation on the face it is very quickly restored by the proliferation of adnexal epithelium of hair follicles and glands. These dedifferentiate and redifferentiate into keratinizing epidermis indistinguishable from the orginal one. This experience has been confirmed in planned experiments by Cillman and his group (13) and especially in the work of Lobitz and his associates (21) They showed that the matrix cells of eccrine glands and of hair follicles restore the lost upper end of these structures and also transform into epidermis which helps cover the defect. Kligman and Strauss (15) lately have published presumptive evidence that, in turn the new epidermis of a planed face may produce new vellus hair follicles. Epstein and Kligman (9 10) also have supported the concept of pluripotentiality and equipotentiality of the cutaneous epithelium

The work in human skin has been supported nicely by animal experiments. Restoration of epidermis from adnexal epithelium is quite generally accepted in animals (3) Montagna *et al* (24) showed that in the skin of hairless mice any part of the pilary complex may produce sebaceous and keratinizing epithelium. Montagna and Chase (25) showed that sebaceous glands are lost completely after application of methylcholanthrene to mouse

skin and are regenerated from follicular sheath epithelium Finally Breedis (6) discovered and Billingham and Russell (4) *confirmed that regenerated epidermis of granulating wounds in rabbits gives rise to numerous hairs by neogenesis*

There is good evidence then that any reproductive epithelial cell of the adult skin is pluripotential and that all epithelia are more or less equipotential Most certainly all of them can form epidermis and should give rise to squamous cell carcinoma under carcinogenic stimulation The real solution of the dilemma must be sought elsewhere There is little doubt that Lever s and others observations of the basic similarity of benign adnexal tumors and basal cell epitheliomas are correct and that this entire group of tumors is basically different from squamous *cell carcinoma*

Tumor and Stroma

If the difference is not in the causative stimulus, nor in the origin and potentialities of the tumor cell itself it might be in the cell s relation to other cells. Experimental cancer research by showing that malignant cells can be transplanted and can be propagated in tissue culture independent of other factors has focused attention almost exclusively on the cancer cell for many years. Only lately a general trend has developed to abandon *this preoccupation with the cancer cell and to study what is* called tumor host relations. One of the facets of tumor host relationship is the histologic relation between tumor cell and stroma Let us look at the relation of cutaneous cancer cells to their host tissue the mesodermal corium

Squamous cell carcinoma from the start is an aggressive lesion that destroys normal structure The connective tissue which it invades produces a vascular and inflammatory reaction which in turn is destroyed by the advancing epithelial growth

Basal cell epithelioma at least in the beginning has a definite mutual relationship with its mesodermal stroma and this relationship *resembles the one normally found* in the adnexa and even more that found in the benign adnexal tumors.

Embryologically wherever a hair germ is formed by the epidermis, there is almost immediately an accumulation of mesodermal nuclei beneath it. As the pilary complex develops, all its components are enveloped in the fibrous root sheath that eventually forms the mesodermal papilla of the hair. This papilla becomes the most important determinant of hair growth. As long as it persists in contact with follicular epithelium a new hair may be formed (94). Once it has been destroyed, for instance by the point of the electrolysis needle, no hair will grow from that root even though most of the epithelium survives.

Benign adnexal tumors always have a well organized stroma of cellular connective tissue. This may give rise to an excess of normal products such as mucoid substances, hyalin, or elastic fibers all of which are present normally in the fibrous sheath of hair follicles and sweat glands. It may also produce abnormal substances such as amyloid, cartilage, or bone. In the latter case cutaneous adnexal tumors may closely resemble the well known mixed tumors of salivary glands and often are diagnosed as mixed tumors of skin.

If one scans older texts of pathology, one finds that considerable space is given to the discussion of tumor stroma. Ribbert (31) in his text of 1904 has a chapter on fibroepithelial tumors of the skin. I have recently revived this term (99) for a small group of peculiar fleshy tumors found usually on the lower part of the trunk or the thighs. These growths often resemble fibromas clinically and may resemble papillomas of the seborrheic keratosis type histologically. It could be shown, however, that actually they are superficial basal cell tumors in which stromal development is so excessive that it makes up the bulk of the tumor and compresses the epithelium into thin septa. Some of these lesions later develop into true ulcerating basal cell epithelioma. I therefore used the designation premalignant fibroepithelial tumors. It must be understood, however, that this term really fits a much larger group of tumors, in principle all benign adnexal tumors of the benign cystic epithelioma type. All trichoepitheliomas for instance consist of organized stroma as well as characteristic epithelium. Many of the solitary ones

may progress to the formation of more aggressive and eventually ulcerating basal cell epithelioma

A similar type of stroma is present in most basal cell epitheliomas. It is modified by the presence of inflammatory infiltrate which signifies host reaction to the malignant qualities of the epithelium. Stroma may be minor in quantity as the epithelial nests get more bulky But it is present usually even around the thin infiltrating cords of epithelioma that seems to grow naked in senile skin in certain tumors. It is also interesting to note that basal cell epitheliomas do not grow in tissue culture where independence from organizing influences of other cell types seems to be essential.

Proposed Definition of Basal Cell Epithelioma

We thus arrive at a new definition of basal cell epithelioma It may be considered the result of a perverted and monstrous adnexal embryogenesis in the not fully competent adult skin either in response to external tumorigenic stimuli or to unknown and presumably innate causative factors. It is an aggressive tumor derived from any part of the equipotential ectoderm of the skin in combination with organized mesodermal stroma It may arise in matrix cells of adult normal structures or in benign adnexal tumors. It preserves, though in pathologically altered form the relationship that adnexal epithelium has to its stroma and therefore is incapable of metastasis although it may be invasive and destructive locally It is n t fully malignant

Darier s simple scheme that we portrayed in Table I thus is changed and becomes somewhat more complicated as shown in Table II This table requires some explanation and forces me to discuss nomenclature and semantics I introduced the term aggressive for want of a better word I certainly do not insist on it There is however need for a term expressing the peculiar position of basal cell epithelioma It definitely is not carcinoma in all the dire sense of the word Many object to the word epithelioma as meaning a tumor derived from surface epithelium I would be willing to accept the term basalioma which is widely used in Europe but is frowned on in this coun

try It may require an open-minded committee on nomenclature to settle these questions.

The definition of the term "malignant" has come under considerable scrutiny lately (cf Leighton 18) A good review of the subject is that by Foulds (12) who points out that there is no sharp dividing line between benign and malignant. There are widely different degrees of malignancy depending on a variety of factors. More malignant strains of cells may arise in benign or less malignant tumors by progression.

TABLE II. Proposed classification of epithelial tumors

	Benign	Aggressive	Malignant
Adnexal	Benign cystic epithelioma	Basal cell epithelioma	Adenocarcinoma
	Hidradenomas	organoid primordial	
	Glandular nevi, etc.		
Epidermal	Epidermal nevi	?	
		Keratoacanthoma	Squamous cell carcinoma
	Seborrheic keratosis		

I have been digressing considerably from the field of histopathology into tumor biology This was done intentionally because I feel there is no other way of arriving at a consistent and meaningful interpretation of carcinoma of the skin. I realize that the new scheme will displease strict pathologists because it makes objective microscopic diagnosis of malignant tumors of the skin difficult. Biologic relations between epithelium and stroma are beyond the ken of the microscopist. They must be deduced by interpretative reasoning from the fixed images we see in our histologic sections. This may seem regrettable to some but appears inevitable as our knowledge progresses.

Table III gives a survey of the large group of organoid tumors of the skin There is an entire spectrum of differentiation from simple hyperplasia to primordial undifferentiated types The lesions are labeled as "resembling" certain normal constituents of the skin rather than "derived from." This description is not only more objective but also appears to be more accurate on the

TABLE III Organoid tumors of the skin

Level of Differentiation		Structure Resembling			
Normal	Epidermal	Sebaceous Gland	Hair Follicle	Apocrine Gland	Eccrine Gland
Hyperplastic	Verrucous (papillomatous) nevus	Nevus sebaceus	Hairy nevus	Apocrine gland nevus	Eccrine gland nevus
Adenomatous	Seborrheic verruca (syn seborrheic keratosis, basal cell papilloma, etc.)	Sebaceous adenoma	Folliculoma	Apocrine cystadenoma	Eccrine poroma
				Syringadenoma papilliferum	Eccrine syringadenoma
				Hidradenoma	Eccrine spiradenoma
			Benign Cystic Epitheliomas		
More or less organoid		Trichoepithelioma		Syringoma solid hidradenoma	
		Sebaceous epithelioma	Fibroepithelial tumor	Cylindroma	Clear cell epithelioma
		Basal cell epithelioma with adnexal differentiation			
Primordial			Basal Cell Epithelioma		Basal cell epithelioma, sole

basis of the concept of pluripotentiality and equipotentiality of all epithelium in the skin.

Seborrheic Keratosis

I call attention in Table III to the empty space at the bottom of the epidermal column. Individual seborrheic keratoses or verrucae may vary widely in the degree of epidermoid differentiation. It is however extremely rare that they become aggressive or really malignant. In the few cases of my own material in which progression to malignancy seemed to have taken place the result was squamous cell carcinoma sometimes of Bowenoid type. The notion that seborrheic keratoses quite frequently develop into basal cell epithelioma is due to misinterpretation of irritated lesions, in my opinion. I will not go into details but will refer you to Lund's fascicle (22, p. 42) in which these lesions are discussed as basosquamous cell epidermal tumors.

Self Healing Squamous Cell Carcinoma

Development away from objective histopathologic standards of diagnosis has taken place in yet another field of cutaneous malignancy. A number of years ago English authors arrived at the conclusion that there are self-healing squamous cell carcinomas of the skin. Two clinical types are recognized (5): the cases of Ferguson-Smith in which a patient develops multiple lesions over a number of years and the keratoacanthoma or molluscum sebaceum which usually is a single tumor. The tumor like keratoses described by Poth in skin exposed to tar and sunlight may constitute a third type. These tumors have in common that they grow rapidly and reach a diameter of a centimeter or more in a few weeks. They then become stationary and in the course of a few months are sequestered and eliminated with the formation of a scar. Histologically a low grade and highly keratinizing squamous cell carcinoma is found. The picture may vary from what is called pseudoepitheliomatous proliferation, itself an interpretative term, to changes repre

senting all the accepted histologic and cytologic criteria of malignancy There is no doubt in any of these lesions that normal tissue is being destroyed and replaced by aggressive new growth Although certain criteria have been established that make the pathologist suspect keratoacanthoma such as a large central keratinized crater buttress formation of the normal epidermis around the tumor and invasion of the epithelial pegs by inflammatory cells, all these criteria are uncertain and may be found in bona fide slow-growing squamous cell carcinomas of low malignancy but with no tendency of spontaneous healing

Diagnosis thus depends on a combination of clinical and microscopic criteria—rapid growth in the presence of low grade of histologic malignancy The biology of the tumor has to be taken into consideration

Melanoma

Some short remarks must suffice for the melanomas. Here changes of concept concerning the derivation of the nevus cell and arguments concerning the epidermal or neuroectodermal nature of the melanocyte have had little influence on clinical or histopathologic diagnosis. A major shift has occurred however in the interpretation of malignant melanoma in children Spitz (59) and Allen (1) have taught us to recognize the juvenile melanoma a lesion that formerly had been diagnosed as malignant but has a good prognosis if removed completely though conservatively Some of these lesions also occur in adults, while no doubt true malignant melanomas do occur in children The juvenile melanoma is an example that astute histopathologic observation combined with clinical follow up and statistical evaluation has an important place in cancer research

Importance of Staining Technics

I should like to close with a few suggestions on how the accuracy of histopathologic diagnosis may be improved by enabling the pathologist to recognize biologic characteristics of a tumor I am looking here to the field of histochemistry in its widest

sense. Rather simple procedures may suffice in some cases, procedures not even considered histochemical by the purist. One of the simplest and very useful methods is staining of elastic fibers. I recommend particularly acid orcein counterstained with Giemsa solution (28) The routine use of this combination in my laboratory has helped me greatly in a considerable number of cases. Elastic fibers have a very distinctive distribution and morphology in normal skin A section stained for elastic fibers permits one to judge destructive invasiveness or on the contrary new formation of organized stroma. The Giemsa solution does not only permit better differentiation of cell types, but stains hyalin, amyloid and mucoid substances distinctly

A well-known procedure is demonstration of the enzyme tyrosinase by dopa or more accurately by tyrosine. This method, of course requires foresight in the preservation of fresh tissue. It permits the recognition of amelanotic malignant melanomas and their differentiation from undifferentiated squamous cell carcinomas and from Paget s disease, be it on the nipple or in extramammary location

Staining for glycogen especially by the PAS method in suitably fixed tissue shows differences between epidermoid squamous cell lesions, which often contain glycogen, and basal cell epitheliomas, which rarely do. It also permits differentiation of basal cell epithelioma from certain benign sweat gland tumors, such as the eccrine poroma (30) because the latter usually contains much glycogen.

Many other methods can be employed with advantage. Our good old stand by the H&E stain remains useful but it needs complementation by modern procedures in many doubtful cases.

I hope I have shown you that histopathology of skin tumors and its relation to the clinical field are far from dry or stagnating Frontiers are changing here as in any other field

REFERENCES

1 Allen A. C. *The Skin A Cli c pathol gic Treatise* C. V Mosby Co., St. Louis, Mo., 1954 Pages 818-858.

– Anderson, N P and Anderson, H E. Development of basal cell

epithelioma as a consequence of radiodermatitis. *Arch Dermatol and Syphilol* *63* 586-596 (1951)

3 Argyris, T S The effect of wounds on adjacent growing or resting hair follicles in mice. *A M A Arch Pathol* *61* 31 36 (1956)

4 Billingham R. E and Russell P S. Incomplete wound contracture and the phenomenon of hair neogenesis in rabbit s skin Nature, *177* 791 79? (1956).

5 Bowman H E, and Pinkus H Keratoacanthoma (molluscum sebaceum). *A M A Arch Pathol* *60* 19-25 (1955)

6 Breedis, C. Regeneration of hair follicles and sebaceous glands from the epithelium from the scars of rabbits *Cancer Research* *14* 575 580 (19 1)

7 Darier J Des épithéliomes primitifs de la peau *Brit J Dermatol* *34* 145 149 (1922)

8 Darier J and Ferrand M L épithéliome pavimenteux mixte et intermédiaire. *Ann dermat l syphilig* 3 385-40? (1922).

9 Epstein, W L., and Kligman, A M The pathogenesis of milia and benign tumors of the skin *J Invest Dermatol* ?6 1 11 (1956).

10 Epstein, W L, and Kligman, A M Epithelial cysts in buried human skin. *A M A Arch Dermatol* 6 15 -415 (19)

11 Quoted in Favre M Josseraud A and Martin J F T meurs malignes cutanées. *Nouvelle Pratique Dermatologique* VI Masson & Cie Paris, 1936 Pages 693-786

12 Foulds, L. The experimental study of tumor progression a review *Cancer Research* *14* 3?7 339 (1951)

13 Gillman, T Penn J Bronks D and Roux M A re-examination of certain aspects of the histogenesis of the healing of cutaneous wounds. *Brit J Surg* *63* 141 153 (19).

14 Juon M Über die metatypischen Formen der Hautepitheliome *Arch Dermatol u Syphilis* *15* 81 96 (1929)

15 Kligman A M and Strauss, J S. The formation of vellus hair follicles from human adult epidermis. *J Invest Dermat* *27* 19-23 (1956).

16 Krompecher E Der drusenartige Oberflächenepithelkrebs. Carcinoma epitheliale adenoides *Beit pathol Anat* 8 1-41 (1900).

17 Krompecher E. *Der Basalzellenkrebs* Gustav Fischer Jena 1903

18 Leighton J Contributions of tissue culture studies to understanding of the biology of cancer a review *Cancer Research* *17* 929 911 (19 7).

19 Lever W F Pathogenesis of benign tumors of cutaneous appendages and of basal cell epithelioma I. Benign tumors of the cutaneous appendages. *Arch Dermatol and Syphilol* 57 679-708 (1948).

20 Lever W F Pathogenesis of benign tumors of cutaneous appendages and of basal cell epithelioma. II Basal cell epithelioma *Arch Dermatol and Syphilol* 57 709-724 (1948)

21 Lobitz, W Jr Holyoke J B., and Montagna, W Responses of the human eccrine sweat duct to controlled injury growth center of the epidermal sweat duct unit. *J Invest Dermatol.* 23 329-344 (1954)

22. Lund, H Z. *Tumors of the Skin Atlas of Tumor Pathology* Section I, Fascicle 2. Armed Forces Institute of Pathology Washington, D C., 1957

23 Macdonald, E. J *Melanoma in Texas among Negroes and Latin Americans* Fourth Conference on the Biology of Normal and Atypical Pigment Cell Growth 1957 in press.

24 Montagna, W Chase, H B and Melaragno, H P The skin of hairless mice I The formation of cysts and the distribution of lipids. *J Invest Dermatol* 19 83-91 (1952).

25 Montagna, W and Chase, H B. Redifferentiation of sebaceous glands in the mouse after total extirpation with methylcholanthren. *Anat Record* 107 83-91 (1950).

26. Montgomery H Basal-squamous-cell epithelioma *Arch Dermatol and Syphilol.*, 18 50-73 (1928).

27 Pack, G T The role of complexion and race on the incidence of pigmented moles and melanomas. *Clinical Conference on Melanoma* M D Anderson Hospital and Tumor Institute Houston, Texas, November 13 1957 In press.

28. Pinkus, H Acid orcein—Giemsa stain (modification of Unna Taenzer method) a useful routine stain for dermatologic sections. *Arch Dermatol and Syphil* 49 355-356 (1944)

29 Pinkus, H Premalignant fibroepithelial tumors of skin. *Arch Dermatol. and Syphilol* 67 598-615 (1953)

30 Pinkus, H., Rogin, J R., and Goldman P Eccrine poroma tumors exhibiting features of the epidermal sweat duct unit. *AMA Arch Dermatol* 74 511-521 (1956).

31 Ribbert, H Geschwulstlehre fur Ärzte und Studierende. F Cohen Bonn 1904

32 Spitz, S. Melanomas of childhood *Am J Pathol* 24 591-610 (1948)

33. Tullis, J L. Triethylene phosphoramide in the treatment of disseminated melanoma. *J Am Med Assoc* 166 3-41 (1958).

DISCUSSION

DR. ROTHMAN I don t quite see why in practically all tabulations the basal cell epithelioma is called an adnexal tumor I particularly think of superficial erythematous basal cell carcinomas of the sur face. There you see so often proliferation downwards of basal cells very far from any adnexal structure and no organoid formation whatsoever These tumors have the same stromal reactions as any other basal cell tumor

DR. PINKUS I thank Dr Rothman for bringing this up, because that is exactly the point I hoped would be brought up. I would like to answer this way When I say adnexal tumor I mean it not as a tumor derived from adnexa but a tumor resembling glands or hairs or whatever it is. Just as in fetal life all adnexa of course are de rived from the basal layer of the epidermis, I believe in adult skin also quite a few of them, if not many are really derived from the basal layer of the epidermis. Thus to a certain degree we are going back to Krompecher who called it adenoid carcinoma of the surface epithelium. I think we have to add one more point to this hypoth esis, which is this. Let us say a carcinogenic stimulus hits the skin. Often it will produce squamous cell carcinoma like that shown here by Dr Suskind and like what we know happens in animals. From then on the epithelial cell becomes transformed into the budding cell of the squamous cell carcinoma It is now determined definitely in the direction of keratinizing epidermoid structure Another cell hit possibly by the same stimulus or possibly by some other stimulus also undergoes a change, but that change is in the direction of forming new adnexal structure It m ght even possibly form a normal hair But since the adult skin probably is not as omnipotential any more as the fetal skin was, it forms rather monstrous hair follicles of the face and that is what we call basal cell epithelioma.

DR. SULZBERGER I would like to recapitulate briefly one part of th s presentation to see if I have understood it It seems that the carcinogenic stimulus can produce from the epidermis and from the adnexa which also come from the epidermis, different types of tu mors. Some of these tumors are a companied by a troma and take adenoid or adnexal forms. Others are unac ompanied by a stroma and take the more basic characteristics of the prickle cell epithel um. That still lea es the mystery of why some go along with their stroma whicl has an inhibitory effect far as metastases are oncerned nd others go along without the stroma and therefore re not inhibited and fully malignant.

DR. PINKUS I gave you only cl nical and histolog al considera tions—pathogenesis was not n my theme

PROGNOSIS PREVENTIVE MEASURES AND TREATMENT OF PREMALIGNANT CONDITIONS AND MALIGNANCIES OF THE SKIN

FREDERICK D MALKINSON

Section of Dermatology Department of Medicine
University of Chicago Chicago Illinois

It may be well to begin this discussion with a classification of premalignant conditions or precanceroses, as they are often called, and primary malignancies of the skin and mucous membranes. The precancerous conditions may be divided into the following groups

1 Lesions characterized by circumscribed tissue changes (*a*) senile keratosis (*b*) cutaneous horn (*c*) leukoplakia (*d*) arsenical x-ray and tar keratoses (*e*) junction nevus melanotic freckle of Hutchinson, and, rarely cellular blue nevus.

2 Lesions showing more diffuse tissue changes ( ) farmer's skin (*b*) xeroderma pigmentosum (*c*) chronic radiodermatitis

3 Benign, usually long-standing lesions which rarely are precursors of cancer (*a*) chronic inflammation (indolent cutaneous ulcers) (*b*) chronic infections (cutaneous syphilis and tuberculosis, fistulous osteomyelitis of underlying bone, etc.) (*c*) benign tumors (epidermal and sebaceous cysts, trichoepithelioma etc.) (*d*) scars (thermal, traumatic etc.)

The primary cutaneous malignancies can be divided into two groups.

1 Carcinoma in situ (*a*) Bowen's disease and (*b*) erythroplasia of Queyrat

2 Carcinoma (*a*) superficial erythematous basal cell carcinoma (*b*) basal cell carcinoma (*c*) mixed cell carcinoma (*d*) squamous cell carcinoma, (*e*) melanoma and (*f*) Paget's disease

Prognosis

PRECANCEROSES

Montgomery (1) has estimated that 20 to 25% of senile keratoses ultimately develop into carcinoma usually of the squamous cell type although such changes may require months or years (Fig 1) The potential malignancy of the individual lesion is closely associated with its rapidity of growth For patients with numerous senile keratoses and especially for those with outdoor



Fig 1 Patient with farmer's skin showing numerous senile keratoses and squamous cell carcinoma on the nose

occupations, there is a good likelihood that additional keratoses will continue to appear and that one or more carcinomas will eventually follow

The prognosis for malignant change in cutaneous horns (Fig 2) approximates that for senile keratosis and again the tumor is of the squamous cell type Montgomery reported the occurrence of carcinoma in 12 of his 85 cases (2)

Leukoplakia may be regarded as the histologic counterpart of senile keratosis as it occurs on the mucous membranes (Fig 3) The early lesions are characterized by opalescent spots which

later become milky white and which are almost invariably benign. *After a period of months or years,* however the surface becomes rough thickened verrucous and fissured and it is in such hyperkeratotic patches that malignant degeneration may be found. As with senile keratosis then leukoplakia may remain benign and show little change for many years, but ultimately squamous cell carcinoma develops in 20 to 30% of untreated



Fig. 2. Cutaneous horn.

patients (3) For vulvar leukoplakia however the incidence of carcinoma varies from 20 to 50% (4,5)

The association of cutaneous carcinoma with arsenical keratoses (Fig 4) was first described by Hutchinson seventy years ago (6) Since that time it has been found that the ingestion of inorganic arsenic (usually as Fowler's solution containing potassium arsenite or as Asiatic pills containing arsenic trioxide) may also be followed by a wide variety of cutaneous carcinomas and carcinomas in situ basal and squamous cell carcinomas, mixed (basal-squamous) cell tumors Bowen's disease and superficial erythematous basal cell carcinomas. About 90% of the arsenical

keratoses eventually undergo malignant change (7) Although the resultant squamous cell carcinomas are often stated to be of low-grade metastases may occur The overall prognosis in these patients is guarded because of the multiplicity of malignant and potentially malignant skin lesions which may be found Arsenical keratoses at mucocutaneous junctions are particularly dangerous. It has also been shown that in individuals who have received inorganic or rarely organic arsenicals there is a higher



FIG. 5 Leukoplakia of the tongue

than normal incidence of visceral cancers arising in the esophagus respiratory tract and genito-urinary tract (8)

Perhaps the earliest contribution to our knowledge of carcinogenesis was Percival Pott s observation in 1775 that scrotal cancer in chimney sweeps resulted from chronic soot exposure In the nineteenth and twentieth centuries clinical observations revealed that skin keratoses and skin cancers also arose from long standing contact with tars pitch and petroleum products (lubricating oils etc.) Tar and pitch keratoses may arise on the skin from a few months to 40 years or more (usually 10 to 30 years) following continued exposure Many of these persist indefinitely and some become malignant The incidence of squa

mous cell carcinomas arising from tar keratoses is greater than for tumors arising from pitch keratoses (9)

In recent years, numerous reports have appeared in the liter ature describing keratoacanthoma (Fig 5) a benign self healing lesion which clinically may simulate tar keratosis or carcinoma. Keratoacanthoma has been reported to occur in patients with occupational exposure to tar and pitch (10 11) and it is possible



FIG. 4 Arsenical keratoses.

that in the past some of these were misdiagnosed as low-grade squamous cell carcinomas. Histopathological examination of these lesions cannot always rule out the possibility of malignant change however and in such cases the tumor must be treated as a skin cancer

The importance of the nevus as a precursor of melanoma has been widely emphasized in the medical literature The poten tially malignant nevi are those which histologically show nevus cell nests at the dermal-epidermal junction. The reported inci

dence of tumors arising from such lesions versus those arising from normal skin varies anywhere from 18 to 100% (19–16). Becker (17) found that only 93 % of melanomas developed from preexisting pigmented nevi. He noted, however, that when the total surface area of the skin is compared with the surface area of the ten to thirty nevi possessed by the average person, melanoma occurs in nevi relatively more frequently than in normal skin. Butterworth and Klauder (18), reviewing 598 cases reported in the literature, found that the percentage of melanomas



FIG. 5. Keratoacanthoma.

arising from preexisting nevi varied accordingly to the location of the tumor: 16.5 on the head, 7 / on the neck, 1 on the trunk, 9 7% on the genital and anal regions, and 59 3% on the feet. In 90 to 30% of melanomas arising from nevi a history of trauma, especially in the form of chronic irritation (as from a belt or clothing strap), or occasionally in the form of puncture wounds, precedes malignant degeneration (18).

Racial factors are also important. The overall incidence of melanoma and of melanoma arising from nevi (13) is lower in the American Negro than in the Caucasian, even though there is some evidence that the Negro possesses about the same average number of nevi as the Caucasian (20).

The melanotic freckle of Hutchinson (Fig 6) is a flat, slowly enlarging pigmented patch which is usually seen in older individuals and from which melanoma arises in about one-third of cases (?1) Rarely too the cellular blue nevus may undergo malignant change (??–?4)

Clinical studies long ago suggested a relationship between the development of skin cancers and chronic sunlight exposure In many individuals exposure to excessive amounts of sunlight over the years results in a severe form of senile atrophy of the



Fig. 6. Melanoma rising in a partially eroded melanotic freckle

skin (farmer s skin") (Fig 1) The skin becomes thin sallow dry wrinkled, slightly scaling and inelastic often freckles, lentigines, and telangiectases are present. The incidence of senile keratoses and carcinomas in these people is exceedingly high. Public Health Service statistics (25) have shown that precancerous keratoses occur six times as frequently in the southern section of the United States as in the northern part, and that the incidence of skin and lip cancer is two and a half times as great in the southern states (at 3 latitude) as in the central states (at 38 lat tude) The more likely occurrence of carcinoma after chronic prolonged sunlight exposure is further supported by statistic gathered for 46 cases of all types of

skin cancer seen in the dermatology clinic of the University of Chicago from 1930-1946 (26) Of these carcinomas 91 1% arose on sunlight-exposed areas and another 2 1% of the cases on partially exposed sites (Table I) Numerous investiga

TABLE I Skin cancers
Distribution according to site

Exposed		Partially exposed		Unexposed	
Site	%	Site	%	Site	%
Face	87 0	Arm	1.2	Back	3.[illegible]
Ear	1.6	Scalp	0.9	Chest	1.[illegible]
Neck	1.6			Abdomen	1
Hand	0 9			Thigh	0.9
Total	91 1		2.1		6.5

tions reviewed by Blum (27,28) have shown that the carcinogenic rays of sunlight are essentially the same as those responsible for sunburn (2800–3100 A in the ultraviolet part of the spectrum)

A dramatic association of sunlight exposure with cutaneous malignancy is seen in xeroderma pigmentosum a rare syndrome in which extreme sensitivity to sunlight in infancy or early childhood results in severe atrophy or farmer's skin after a few brief exposures. Keratotic and warty growths subsequently appear on the skin and many of these become malignant At a later date basal cell and squamous cell carcinomas arise on exposed skin sites and occasionally melanomas and even angiosarcomas develop Although some patients survive into adult life the syndrome almost invariably terminates in death from metastatic cutaneous malignancy Since xeroderma pigmentosum is inherited as a recessive trait (29) it provides an excellent illustration of a link to genetic factors as well as to sunlight exposure in the pathogenesis of skin cancer

Chronic radiodermatitis resulting from overexposure to x rays of almost any modality or to sources of spontaneous radioactivity is not infrequently the site of premalignant keratoses or of cutaneous malignancies. Carcinoma usually of the squamous

cell type may develop from one or more x ray keratoses or at the sites of persistent radiation ulcers, although squamous cell carcinoma or less often basal cell carcinoma (30) may arise de novo anywhere within the area of radiodermatitis Saunders and Montgomery (31) found only one carcinoma in patients with first degree (mild) skin injury but 17 4% of patients with second degree (moderate) and 30% with third degree severe radiation skin changes developed cutaneous cancers. In general malignant change in the skin after radiation damage in excess of that required to produce simple telangiectasis occurs in about 20% of patients.

Rarely certain benign lesions, usually of long standing are the sites of cutaneous carcinoma. Squamous cell carcinoma may arise at the edge of indolent ulcers (stasis ulcer for example) although one has to distinguish this tumor histologically from pseudo-epitheliomatous hyperplasia a benign nonspecific, proliferative imitator of squamous cell carcinoma In one series of 386 cases of carcinoma of the extremities, six were found to have developed in varicose ulcers (32) DeAsis found only one malignancy in 310 cases of varicose ulcers (33) Carcinoma has also been reported very rarely to arise in decubitus ulcers, third degree burns, atrophic scars of chronic discoid lupus erythematodes, and ulcerations complicating both acrodermatitis chronica atrophicans and scleroderma (3)

Skin and mucous membrane cancers occasionally complicate certain infectious disorders. In the past leukoplakia and carcinomas of the mouth especially of the tongue were not an uncommon complication of tertiary syphilis (34 35) Lupus vulgaris, an indolent form of reinfection tuberculosis, has been reported to be the site of complicating carcinoma in 0.5 to 4 0% of cases (3).

Epidermal cysts and sebaceous cysts, commonly called wens, may on rare occas ons be the sites of malignant change Carcinoma occurs in about 1.5% of epithelial cysts (36) usually in the form of squamous cell carcinoma arising from an epidermal cyst. Malignancy is of a relatively low order in these lesions and metastases seldom occur (37) Basal cell carcinoma may arise in

sebaceous cysts but its occurrence is most unusual and probably coincidental (36)

Although the percentage of incidence is low scar tissue is the site of cutaneous cancer more frequently than any other type of benign circumscribed skin lesion Burn scars are most frequently affected (Marjolin s ulcer) (33) Treves and Pack (38) estimated that in burn scars the incidence of squamous cell carcinoma is 2% and the incidence of basal cell carcinoma 0 3 %. The likelihood of development of carcinoma in a burn scar is



Fig. 7 Bowen disease

inversely proportional to the age of the patient at the time of the burn (33) Once a carcinoma arises in scar tissue it grows slowly as long as it remains confined to the scar itself but the tumor often becomes rapidly invasive after extension into normal adjacent tissue

CARCINOMA IN SITU

For Bowen s disease (Fig) and for erythroplasia of Queyrat both indolent persistent disorders, the incidence of complicating squamous cell carcinoma is 9% (40 41) For erythroplasia of Queyrat malignant change occurs sooner than in Bowen s

disease and metastases to the regional lymph nodes occur relatively early

CARCINOMA

Skin carcinomas generally have a far better prognosis than malignant growths in any other tissue or organ Steiner's survey (49) in 1952 showed that carcinomas of the skin accounted for only 2.2% of all cancer fatalities in the United States. As low as this figure appears to be, however the possibility for early diagnosis of tumors arising on the skin surface and the accessi



FIG. 8 Nodular basal cell carcinoma.

bility of these lesions for adequate therapy should some day eradicate the mortality from skin cancer altogether

Superficial erythematous basal cell carcinoma is usually multiple and often occurs on the trunk Although it is a more benign form of basal cell tumor invasion of the dermis and underlying structures by detached tumor cells occurs in some cases, and the prognosis is then that of basal cell carcinoma.

Basal cell carcinomas (Figs. 8–10) which comprise about 65% of all cutaneous malignancies, are characteristically slow growing and respond most satisfactorily to adequate therapy if the tumor is not too far advanced Spontaneous remission of a basal

cell carcinoma however is an extreme rarity The course of the untreated lesion is relentless with slow but persistent local peripheral and invasive growth. Extensive tissue destruction—especially of large areas of the face—hemorrhage and complicating infections are all frequent accompaniments of the far advanced tumor In the late stages deep invasion of bone particularly with involvement of structures such as the orbit or the cranial cavity usually makes it impossible to save the patient.

Metastases from basal cell carcinomas occur very rarely but when encountered may ultimately be fatal Lattes and Kessler



FIG. 9 Ulcerated basal cell carcinoma forehead

reviewed eighteen such cases recorded in the literature and added two patients of their own (43) In some of these cases dissemination was confined to the regional lymph nodes but several patients showed widespread visceral especially pulmonary metastases at the time of death

About 15% of cutaneous cancers are squamous cell carcinomas (44) (Figs. 1 11–13) These tumors are faster growing than the basal cell carcinomas and may metastasize to the regional lymph nodes and beyond to other tissues and organs. One-third of the lesions are found on the lower lip where the prognosis is not so good as for cutaneous tumors. Intraoral carci

nomas are not infrequent and squamous cell carcinomas may also arise on the genital and anal mucous membrane surfaces.

The outlook depends in good part on the histopathologic estimation of malignancy which is usually based on Broder's method of grading as follows

Grade	*Differentiated Cell %*	*Undifferentiated Cells, %*
1	75 to 100	25 to 0
2	50 to 75	50 t 25
3	25 to 50	75 to 50
4	0 t 25	100 t 75



FIG. 10 Morphea-like basal cell carcinoma

Squamous cell carcinomas of the skin are often well differentiated and in a series of 507 such tumors, Warren and Hoerr (45) classified 383 (or 75%) as showing the lowest grade of malignancy Metastases from cutaneous lesions do occur however and Ackerman and del Regato (46) reviewing 70? cases, reported metastases in 87 patients (12%). Other factors affecting prognosis are the size of the lesion duration, location (the outlook is poorest for intraoral lesions) and failure of previous therapeutic measures.

Melanomas (Figs. 14–17) comprise about 5 to 9% of the primary tumors of the skin (4 ?4) and are easily the most

malignant of these growths. Untreated melanomas are uniformly fatal following incredibly widespread metastases via the lymphatics and blood stream. Involvement of organs not usually the site of tumor dissemination (such as the heart and spleen), spread to other tumors (as in the breast or uterus) (47) and transplacental metastases (48 49) have all been recorded. For melanomas of the mucous membranes the prognosis for survival is negligible even with therapy (50 51). There is little hope for



Fig. 11 Squamous cell carcinoma

previously treated recurrent lesions and those in sites drained by multiple lymph channels. Similarly the outlook is extremely poor for pregnant women with melanoma since pregnancy seems to promote an even more rapid growth and dissemination of the tumor (52). Apart from the pregnant state however Allen and Spitz (50) studying 337 cases found that the survival rate for females was twice that for males.

There are two circumstances in which the prognosis for melanoma is somewhat improved. It is clear that the incidence of the malignancy is quite low in prepubertal patients. The histologic appearance of seemingly malignant lesions in children can often be readily distinguished from the truly malig

nant and potentially metastasizing melanoma, and the microscopic features of juvenile melanoma upon which this distinction is based have been described in detail (22,50,53) Only on rare occasions does metastatic melanoma occur in prepubertal individuals (50,54,55) The prognosis is somewhat better too for the more slowly growing and later metastasizing lesions arising from the melanotic freckle (?1)

In Paget's disease the clinical appearance is usually that of

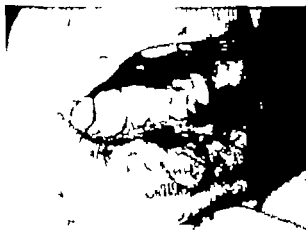


FIG. 12 Squamous cell carcinoma of the lip.

a sharply circumscribed eczematous patch surrounding the nipple. These skin changes, which present typical histologic features, are not in themselves malignant but invariably accompany or presage an intraductal carcinoma of the breast Even in the absence of a palpable tumor in a histologically proven case of epidermal change immediate surgical intervention is indicated since these patient almost invariably have microscopically apparent intraductal carcinoma For the untreated patient the overall prognosis is that of intraductal carcinoma of the breast and the outlook is serious in patients already showing axillary node involvement (56) Rare cases of extramammary Paget's disease usually accompanied by apocrine gland carcinoma have also been reported (57,58)

Prevention

The prevention of precancerous and cancerous lesions means essentially the avoidance or removal of those factors producing chronic skin or mucous membrane irritation It may be advisable for example to acquaint young individuals who have outdoor occupations but as yet show little skin change with the consequences of long term sunlight exposure This is particularly important for individuals with blue eyes and fair complexions living in southern latitudes An effective sunscreen



FIG. 13 Squamous cell carcinoma on the dorsum of the hand

preparation such as 15% *p*-aminobenzoic acid ointment which screen out rays in the range of 2800–3100 Å can be prescribed for times when sun exposure is unavoidable This preparation is particularly important for those patients already showing the changes of farmer's skin and who cannot or will not leave their outdoor jobs In all these individuals, moreover recreational sun exposure should be strictly curtailed Therapeutic ultraviolet light and as a rule x ray irradiation to affected skin areas for any purpose is contraindicated as is the use of photosensitizing substances such as tar It is important that patients

with senile keratoses and those with farmer's skin as well as patients with the other diffuse tissue changes (chronic radiodermatitis, xeroderma pigmentosum) have regular periodic medical examinations. Any lesion showing suspicious changes (redness and induration at the base of a keratosis, for example) should be biopsied, as should all new lesions suspected of being malignant.

The appearance or recurrence of leukoplakia may be pre



FIG. 14 Melanoma.

vented by prompt attention to any factors inducing mucous membrane irritation Ill fitting dentures, faulty occlusion carious and broken teeth and improperly constructed crowns and bridges should all be corrected, and habitual chewing of the lip or buccal mucous membranes should be discouraged It is extremely important to prohibit smoking in any form in all individuals who have once developed leukoplakia. Chronic sunlight exposure is a significant etiologic factor in leukoplakia of the lower lip and protective measures similar to those just discussed especially the use of a sunscreen ointment can be recommended particularly for individuals with recurrent leukoplakia.

The relatively low incidence of late syphilis following the advent of penicillin therapy has reduced to some extent the incidence of oral leukoplakia especially of the tongue

In the matter of occupational cancer preventive control methods are of great importance Industrial processes associated with formation of tar fumes or pitch dust should be entirely enclosed or performed near suction hoods. In other industries and in laboratories workers must be thoroughly protected against cu



Fig. 15 Melanoma

taneous exposure to x rays and to sources of radioactivity All employees in industries where there may be exposure to r contamination of the skin with potential carcinogens should be furnished clean work clothes and be instructed to take a thorough shower bath at the end of each working day Protective work clothing should also be available where needed Frequent medical examination of the workers should be performed and all suspicious skin lesions should be fully evaluated and treated as indicated. Occasionally despite precautions individuals exposed to occupational carcinogens (tar pitch petroleum deriva

tives, arsenicals, etc.) may finally be forced to change their jobs, although industrial control methods in this country at the present time are very good.

Since sites of chronic infection or inflammation especially ulceration, may give rise to malignant lesions, the best method of tumor prevention here is obviously adequate therapy of the underlying condition

The significance of trauma in the development of melanomas

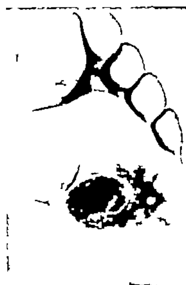


FIG 16 Ulcerated melanoma

from preexisting nevi has already been discussed Any nevus which is subject to chronic irritation from articles of clothing or from other causes should be surgically removed

Since arsenicals, and particularly the inorganic compounds, have been implicated in the production of a wide variety of premalignant and malignant disorders of the skin as well as malignancies in other organs, arsenical medication should be administered as indicated only to patients with potentially fatal diseases.

The prevention of cutaneous carcinomas is practical only in-

sofar as we can recognize and eradicate etiologic factors, such as chronic sunlight exposure intermittent trauma and chemical cancerogenesis and adequately prevent treat or keep under constant surveillance the various premalignant conditions The first group of factors has already been discussed here and in a previous paper Since the prevention of carcinoma arising from the precanceroses is largely a matter of treating these premalignant lesions, the therapy of these conditions and of malignant lesions of the skin will now be reviewed



Fig 1 Metastatic melanoma of the skin.

Treatment

PRECANCEROSES

Measures suitable for the treatment of senile keratoses depend on the history and appearance of specific lesions. The small keratosis (2–4 mm) which has shown no growth or surface change may be left untreated provided the patient returns regularly for observation Often a keratolytic ointment such as 3% salicylic acid in unguentum aquae rosae applied two to three times daily removes the hyperkeratotic scale although it does not correct the underlying cellular alterations. When a keratosis persists and particularly when it enlarges becomes widely ery

thematous, or begins to show infiltrative changes, biopsy followed by electrodesiccation and curettage is indicated If malignant change has occurred, further treatment is carried out as described below Therapeutic measures taken for arsenical tar and x ray keratoses are essentially analogous to those for senile keratosis.

Cutaneous horns should be routinely biopsied and destroyed by electrodesiccation For large lesions, however surgical excision is preferable. When thoroughly removed by either method cutaneous horns seldom recur When carcinoma is found histologically treatment is carried out as described for squamous cell carcinoma

In patients with leukoplakia initial biopsy of all lesions is advisable. If the patches are still flat and opalescent correction of local irritant factors (mechanical irritation smoking sunlight exposure) together with continued observation suffice. Persistent leukoplakia or lesions which become rough and thickened should be biopsied at sites which appear most advanced and then should be treated by thorough electrodesiccation Surgical excision is also a satisfactory method of treatment, although it is somewhat elaborate for very small lesions. Again preventive measures must be instituted and not infrequently patients remain free of recurrence. The careless patient is prone to relapse however and requires close medical observation at 2 to 3-month intervals with repeated removal of recurrent lesions. The rare patient with leukoplakia and syphilis is given antisyphilitic therapy but this has little effect on the leukoplakia and must be combined with appropriate local measures.

When squamous cell carcinoma is found after biopsy of a patch of leukoplakia surgery or radiation therapy is indicated with removal of lymph nodes which may be involved For persistent widespread leukoplakia of the lip with or without carcinoma, a satisfactory surgical procedure is a wedge or horizontal resection with outward extension of the mucous membrane of the inner lip to produce a new vermilion border

Patients with vulvar leukoplakia may also be treated by electrodesiccation or surgical excision Because of the high incidence

of squamous cell carcinoma in these patients close medical observation is imperative. Unfortunately erroneous diagnoses of vulvar leukoplakia are not infrequent and are often followed by surgical vulvectomy It is extremely important that primary atrophy of the vulva, senile genital atrophy lichen sclerosus et atrophicus (kraurosis vulvae) and circumscribed neurodermatitis of the vulva all be carefully distinguished from the hypertrophic process of leukoplakia (59) Obviously the prognosis and the therapeutic management of each of the former conditions is quite different from leukoplakia and needless radical surgery must be avoided Where clinical differential diagnosis is difficult *biopsy should be performed It must be emphasized however* that while leukoplakia often develops on previously normal mucous membrane surfaces, it may also arise as a complication of primary atrophy of the vulva or lichen sclerosus et atrophicus.

The number of junction nevi possessed by the normal individual (about 20) *is far too large to warrant their prophylactic* removal Although some have advised excision of lesions situated at pressure points—palms soles, etc —even this is not often feasible. It is imperative however to remove surgically any nevus that is subject to selective chronic or intermittent irritation (as from a comb a belt, a razor or a clothing strap) and those irritated by friction in intertriginous locations. Furthermore any nevus which shows suspicious clinical changes should *be excised at once The changes which may accompany the devel*opment of melanoma in a preexisting nevus are one or more of the following: rapid increase in size darkening of color development of satellite pigmentation erythematous inflammatory halo, erosion crusting bleeding ulceration and occasionally subjec*tive symptoms of itching or irritation.* The importance of suspecting melanoma clinically is emphasized by Becker's statistics (17) showing that less than half of the microscopically proven melanomas are diagnosed correctly prior to *biopsy For a large* ulcerated and clinically clear-cut melanoma the excision should be therapeutic meaning excision down through fascia with the widest possible margin Smaller lesions especially where recent trauma with subsequent hemorrhage and crusting leaves the

diagnosis in doubt can be fully excised but more conservatively If the suspicion of melanoma is confirmed microscopically radical reexcision of the involved area is carried out.

The melanotic freckle of Hutchinson should be removed in the absence of melanoma preferably by surgical excision although electrodesiccation here may be satisfactory (21) Where melanoma is present wide and deep surgical excision of the tumor together with the pigmented patch is indicated. Involved lymph nodes are also surgically removed in the absence of distant metastases.

Measures for the treatment of patients with farmer s skin have already been discussed in part. Avoidance of sunlight and the use of sun-protectant preparations are essential. The regular use of a bland emollient cream may also be helpful Keratoses are treated as described above and any skin lesion suspected of being carcinoma should be biopsied and treated accordingly In general it is best to avoid x-ray therapy to affected areas. Medical reexamination of the skin should be carried out for these individuals every three to six months.

The treatment of radiodermatitis is somewhat similar to that for farmer s skin Soft creams for dryness and scaling are advisable as well as the use of a sunscreen ointment and avoidance of sunlight exposure X ray keratoses should be biopsied and removed by electrodesiccation even though healing may be slightly delayed. Any new growth in affected areas should be promptly biopsied and treated. Therapy for chronic radiation ulcers is combined with continuous observation for the possible development of carcinoma in these lesions. If persistent, the ulcer can often be totally excised. Where feasible, especially for small areas of radiodermatitis or for areas where keratoses and skin tumors are repeatedly arising surgical removal of all affected skin with or without skin graft should be considered.

Needless to say further radiation therapy to areas of radiodermatitis is contraindicated and all carcinomas are treated by surgical or destructive means. Even very small x ray exposures, for example diagnostic dental films in a patient with circumoral radiodermatitis are contraindicated except for emergency situ

ations. Again all these patients should be regularly examined at 3- to 6-month intervals.

Patients with xeroderma pigmentosum are treated in a manner analogous to that described for farmer's skin. Extremely strict avoidance of sunlight, prompt surgical removal of all keratoses and tumors, and very close medical supervision are imperative here. Interfamilial marriages in such patients should be strongly discouraged.

The treatment of benign long-standing lesions which are occasionally premalignant cannot, of course, be discussed in any detail here. It is sufficient to say that appropriate dermatological, medical, or surgical therapy is indicated for these various lesions, and that any superimposed new growths should be biopsied. Indolent ulcers should be frequently reexamined clinically for possible tumor formation during therapy. Burn scars can be kept under surveillance at 6- to 12-month intervals, and small scars may be surgically excised.

For the rare carcinomas arising within epidermal or sebaceous cysts, surgical removal of the cancer and the cyst is the treatment of choice. Surgical excision is also the preferred method of treatment for tumors arising in scar tissue, and where feasible, the scar itself should always be included.

CARCINOMA IN SITU

Bowen's disease can be treated by surgical excision or by electrodesiccation. For very large or multiple lesions where surgery is not practical, electrodesiccation is the method of choice and this procedure can be carried out in stages. X-ray irradiation is not entirely reliable for Bowen's disease and is not recommended. For a lesion in which invasive squamous cell carcinoma has already arisen, surgical excision is the preferred treatment method and should include the area of dermatosis whenever possible.

Treatment for erythroplasia of Queyrat is analogous to that recommended for Bowen's disease. As always, however, it is extremely important here to biopsy the lesion initially. Sachs and Sachs (60) and later Zoon (61) called attention to the syndrome

named by Zoon "chronic circumscribed balanoposthitis," a condition clinically indistinguishable from erythroplasia of Queyrat. Histologically, however, this disorder shows only inflammatory changes, and the patient often responds favorably to topical therapy. For true erythroplasia surgery can be performed for suitably situated lesions (for example, circumcision for foreskin involvement), but in other locations such as the glans penis electrodesiccation is the only feasible treatment. Unfortunately, recurrences are frequent after electrodesiccation so that close observation of the patient and, not infrequently, retreatment are necessary. When squamous cell carcinoma is found, it should be surgically excised, and often partial or complete penile amputation may be required along with removal of involved lymph nodes.

CARCINOMA

There are several acceptable treatment methods for superficial erythematous basal cell carcinoma. Where lesions are few and relatively small, surgical excision is recommended. For numerous lesions and especially for patches measuring several centimeters in diameter, electrodesiccation with curettage can be done in stages. Standard dermatologic x-ray therapy is successful in treating these lesions, but considerable radiation penetrates to normal tissue below the tumor. Good treatment results may be obtained, however, with very soft (Grenz) rays (69) which are largely absorbed by the epidermis and the attached tumor cells. Because of the tendency for new lesions to continue to develop, patients with superficial erythematous basal cell carcinomas should be periodically reexamined.

When invasive basal cell carcinoma develops from the superficial erythematous type, both lesions can be treated by standard dermatologic x-ray therapy or by surgical excision. Grenz ray therapy is inadequate treatment for invasive lesions because the depth of these tumors in tissue exceeds the penetrability of this type of radiation.

The therapy for previously untreated basal and squamous cell carcinomas of the skin resolves itself essentially into one of two

choices x ray irradiation or surgical excision The choice of treatment depends on the size and location of the tumor on the presence or absence of metastases, and for the recurrent lesion on the history of previous treatment. X ray therapy has the advantage of destroying carcinomatous tissue selectively without mutilation while surgery in certain sites about the face such as eye canthi and ala nasi is difficult or may have disfiguring effects. Furthermore x ray therapy avoids the necessity of a surgical procedure and this may be advantageous particularly in elderly or ill patients. The use of x rays is also the only practical method for dealing with involvement of deeply situated tissues inaccessible to surgery

Surgical removal is the preferred method of treatment where a radical procedure is necessary to assure patient survival i e for large rapidly growing squamous cell tumors and for those complicated by regional lymph node metastases. Surgical excision is also advantageous where prompt removal with a single procedure is desirable since fractionation of x ray therapy requires more prolonged treatment periods.

Surface or interstitial application of radium has also been used successfully for the treatment of skin cancers (63 64) Most observers feel however that x ray therapy is more accurate in extent and depth of treatment than interstitial radium In addition the preparation and use of special molds for surface radium therapy is unquestionably time-consuming

Electrodesiccation with curettage is an unreliable form of treatment and lacks the opportunity for histologic control of removal afforded by surgery Scar formation from this method is also generally unsatisfactory Electrodesiccation is useful however for the treatment of small usually multiple recurrent carcinomas at sites where further x ray therapy or surgery is not practical

The local use of caustics is to be condemned except in expert hands for the rarely indicated special technique developed by Mohs (65) for far advanced destructive lesions.

The author's own preference for treatment of skin cancers is x ray therapy With competent techniques this method has an

extraordinary degree of adaptability is without significant trauma or discomfort to the patient and is the only satisfactory form of treatment for lesions which are difficult to remove surgically Cosmetic results, too, are usually quite acceptable Both basal and squamous cell carcinomas respond very well to x ray therapy and these lesions can usually be treated with equivalent dosages of radiation.

When x ray therapy is used a margin of at least 4–6 mm of seemingly uninvolved skin should be included about the circumference of the irradiated area. Fractional dosages are routinely used the amount of radiation given at each treatment depending on the size and location of the tumor Since 1947 our method of treatment has been to give 5400 r in equal fractional doses administered three times weekly until a total of nine treatments has been given (9 $\times$ 600 r) Small lesions over ample subcutaneous tissue are sometimes treated in five sessions. For lesions on thin skin overlying bone or cartilage (such as the ear) and for those measuring over 2 cm in diameter daily treatments of 360 r each are given five days a week for three weeks (15 $\times$ 360 r) The factors for the radiation administered are TSD 70 cm 80 kv 10 ma (inherent filtration 0 71 mm Al)

The case records of 68 patients treated for all types of skin carcinomas with x rays or radium at the University of Chicago Clinics from 1945 to 1950 have been reviewed (66) To these were added the case histories of 6 patients treated between 1938 and 1945 In all 78 carcinomas were treated in this group of 74 patients. There were 36 basal cell carcinomas, 11 squamous cell carcinomas 8 intermediate (variant of basal cell) carcinomas 5 mixed cell carcinomas 11 squamous cell carcinomas in situ and 7 superficial erythematous basal cell carcinomas In all patients the diagnosis was confirmed or established by biopsy and all cases were followed for at least five years. Of these tumors 71 were treated successfully without recurrence although many received therapeutic dosages now recognized as frequently inadequate Of the 7 recurrences noted (all basal cell carcinomas) 6 occurred in patients receiving insufficient x ray treatment (1800–3600 r) One recurrence was seen in a patient who had received 4500 γ radium which also is now considered an inade-

quate dose Of the 46 patients treated with the modern dosage schedule of 5400 r or an approximately equivalent dose of radium therapy none showed recurrent tumor growth

The treatment results in this last group of patients compares well with the five year cure rate of 98.9% recorded by Andrews *et al* (67) for a similar series of 94 patients treated with modern x ray dosage schedules The importance of following all treated patients for at least five years cannot be stressed too strongly Our own practice is to see the patient at 3-month intervals in the first year after treatment at 6-month intervals in the second year and at yearly intervals thereafter

Where surgical removal of skin tumors is performed scalpel excision is preferred to electrosurgery so that the specimens remain intact for microscopic examination The excision should be of adequate depth and include a margin of 0.5 cm of normal tissue beyond the border of the tumor If the carcinoma arises from a premalignant lesion the latter should also be included in the excision as discussed above More radical removal is indicated for recurrent carcinomas and on the extremities far advanced, widely destructive lesions may require amputation.

Treatment statistics reported in the literature for numerous series of patients are difficult to evaluate because of wide differences in therapeutic methods and loss of elderly patients from intercurrent disease The general experience however is that 95% cure rates or better can be achieved with basal cell carcinomas, although for squamous cell carcinomas the cure rates are lower The worst prognosis is in those patients with far advanced locally destructive lesions, those with metastases, and those with recurrences at the sites of previously treated lesion

The prognosis for skin carcinomas is the best for any malignancy affecting humans although it is still too frequently compromised by inadequate therapeutic techniques or too long delay on the part of patients in seeking treatment Ideally and in actuality 100% of these tumors are curable By modern techniques of irradiation therapy this goal is almost within reach

The treatment of carcinomas of the lip and mouth cannot be presented in detail here In general the squamous cell carcinoma of the lip grows more rapidly metastasizes more readily

(about 20% of cases) and offers a poorer prospect for cure than the cutaneous squamous cell carcinoma. For carcinoma of the lower lip x ray therapy is usually the preferred method although surgery is the treatment of choice for large tumors, for those previously treated by inadequate irradiation and for carcinomas which have metastasized to regional lymph nodes. The prognosis depends largely on three factors the size of the lesion at the time of treatment, its histologic classification according to cellular differentiation and the presence or absence of metastases. For lesions without metastases treated surgically or by x ray irradiation the five-year cure rates in many series range as high as 80 to 95% (68–71). With metastatic lymph node involvement, however the five year survival rates are in an approximate range of 20 to 50% (72) In contrast to lower lip involvement carcinoma of the upper lip is rare, metastasizes more readily *and has a worse prognosis.*

The average intraoral carcinoma is far more malignant than carcinoma of the lip and the prognosis is worst for tumors on the posterior tongue the inferior gingiva the floor of the mouth the soft palate and the faucial region On initial examination metastases may be seen in 60% or more of carcinomas in these last locations. The treatment methods of choice depend upon the size and location of the tumor and are limited here essentially to interstitial radiation with radium or to surgical excision. Interstitial radiation can be used advantageously for the treatment of carcinoma of the tongue floor of the mouth and buccal mucosa while surgical excision is preferred for certain gingival lesions and those of the hard palate. Surgical removal is also the recommended treatment procedure for lymph nodes with metastases.

With the possible exception of carcinoma of the soft palate the role of x ray therapy in the treatment of intraoral carcinomas is a very limited one in contrast to its great usefulness for skin and lip cancers

The overall cure rate for squamous cell carcinomas of the mouth seldom exceeds 50% and for most anatomical sites, particularly in the presence of metastases, it is far lower For all cases of intraoral carcinoma Taylor and Nathanson (75) reported

cure rates ranging from 14% for carcinoma of the tongue and 17% for carcinoma of the floor of the mouth to 45% for tumors of the hard palate

The treatment of *choice for melanoma is surgical removal of* the tumor Since melanoma cells are radioresistant x ray therapy has only rarely been used and then usually in extremely high doses equivalent to cauterization Ancillary methods of treatment such as hypophysectomy adrenalectomy and the use of hormonal agents are apparently not of significant value

For the clinically obvious or microscopically proven mela*noma local surgical excision should be radical* usually necessitating a skin graft for closure Careful microscopic examination of the excised tumor must be carried out to give assurance of complete removal since inadequate excision will inevitably be followed by local recurrence metastases and death Amputation may be preferable in an extremity where the extent of excision is apt to produce crippling deformity or where a toe or finger *is involved However the extremely radical en bloc excisions* of primary tumors draining lymphatic channels and regional nodes are gradually being abandoned for two reasons (*a*) metastases have often already occurred through deep lymphatic channels and beyond the regional nodes as well and (*b*) there is no objective evidence as yet that cure rates are enhanced by such procedures (50)

In the absence of distant metastases involved regional lymph nodes should always be excised For tumors about the head and neck with cervical node involvement the prognosis is relatively better than for lesions of the lower extremity for example where deep inguinal and iliac nodes are usually involved Although prophylactic lymph node resection in the absence of palpable enlargement has been widely recommended there is considerable disagreement *on the efficacy of this procedure* Staley (74) found microscopic involvement of the nodes in only 2 of 37 cases subjected to prophylactic resection and Clarke (77) in a study of 90 patients with melanoma, found no difference in survival rates in patients subjected to prophylactic nodal resection as compared with patients in whom the nodes were removed only after clinical enlargement On the other hand Pack and

Livingston claim that clinically undetectable melanoma is found in the excised nodes of 50% of their patients (76) Weighing the available evidence, one might conclude that prophylactic removal of lymph nodes may be carried out in regions where these structures are accessible (cervical or axillary) However where lymphatic drainage from lesion may lead to lymph nodes situated at widely separated sites such as the axillae and groins (as may be the case for lesions in the midline of the upper abdomen or in the midline of the back) this procedure is unwarranted.

The prognosis for survival in patients with melanoma depends on the extent of involvement at the time of initial examination although the clinical course may be vicarious in any given case. Individuals with clear-cut metastases beyond the regional lymph nodes are considered to have a hopeless outlook and surgical intervention is not indicated. Of the patients with regional node involvement 5 to 30% survive five years after therapy the better prognosis being reserved for those showing histologic but no clinical evidence of nodal metastases. In patients without microscopic involvement of the lymph nodes, survival rates rarely range to 50% or higher the best outlook being in those lesions showing only very early tumor invasion of the underlying dermis [the superficial melanocarcinoma of Allen and Spitz (50)]

Several additional factors modify the prognosis. Five year cure rates for melanoma are a notoriously inaccurate index for long term survival (77 78) Allen and Spitz (50) reported that 13% of a series of 500 fatalities occurred in patients who died of their metastases five years or longer after initial diagnosis and treatment. Another important factor is that in approximately 1 to 4% of patients, multiple primary melanomas may develop (50 79) The size of the lesion and the presence or absence of ulceration when first seen also affect the outlook for survival after treatment The sex of the patient is of significance since in some series (50 75) it has been shown that the survival rate for women is far better than for men Additional factors governing prognosis (pregnancy location of tumor type of preexisting lesion previous inadequate therapy etc.) have already been discussed above

Some representative results following treatment of melanoma are as follows. In 623 cases Allen and Spitz (50) found five year plus survival rates ranging from 12.8 to 39.8% in females where the patients were classified according to age by decades. Five-year survival rates for male patients ranged from 5 to 16.7%. In 68.3% of all patients surviving five years or more, treatment consisted only of local excision of the tumor. Meyer (80) reported a five year survival rate of 41.5% in 65 patients. Of the 65 patients 40 had lymph node dissections. 19 of the 40 had negative nodes with a five year survival rate of 66.7%; 21 of the 40 had positive nodes with a five year survival rate of 33.4%. Pack *et al.* (51) reported an overall five year survival rate of 9.7% for 525 patients, although a large number of these were treated initially for recurrent melanoma which of course has a worse prognosis than the initial tumor. Five years after surgery 17.7% of patients without nodal involvement and 15.6% with metastases to the regional nodes were alive. Clarke (75) reported a five-year survival rate of 46% in 37 patients in whom only local excision of the melanoma was performed, and a 40% survival rate in 53 patients with regional node resections, metastases being found in 33 of these. Brandt (24) reported a five year uncorrected survival rate of 20.5% for a series of 112 patients.

In the treatment of Paget's disease prompt diagnosis is essential even in the absence of a clinically palpable tumor. Although biopsy is desirable immediately, the nipple and areola are not uncommonly the site of eczematous eruptions which clinically may be indistinguishable from Paget's disease. Where there is sufficient doubt as to the diagnosis a two-week trial period of topical dermatologic therapy is sometimes warranted in the absence of a mass in the breast or enlarged non tender axillary nodes. If there is no clinical response within that time, biopsy should then be performed.

A discussion of the treatment of carcinoma of the breast is obviously beyond the scope of this paper. As a rule, radical mastectomy is the procedure of choice where feasible. The prognosis is that for intraductal carcinoma of the breast with five year survival rates appreciably lower in those patients with metastases to the axillary nodes.

REFERENCES

1 Montgomery H Precancerous dermatosis and epithelioma in situ. *Arch. Dermatol and Syphil L 39* 387 (1939)
2. Montgomery D W Cornu cutaneum. *Arch Dermatol and Syphilol. 44* 231 (1941).
3 Mackee G M and Cipollaro, A. C. Cutaneous cancer and precancer A practical monograph. *Am. J Cancer* 1937
4 Ormsby O S. and Montgomery H *Diseases of the Skin* 8th edition Lea and Febiger Philadelphia, Pa., 1954
5 Taussig, F J Leukoplak c vulvitis and cancer of the vulva. *Am. J Obstet Gynecol. 31* 746 (1929).
6. Hutchinson, J Arsen c cancer *Brit M d J* 2 1280 (1887)
7 Montgomery H Arsenic as an etiologic agent in certain types of epithelioma Differential diagnosis from, and further stud ies regarding, superficial epitheliomatosis and Bowen s dis ease *Arch Dermatol and Syphilol. 32* 218 (1935)
8. Sommers, S. C., and McManus, R. G Multiple arsenical cancers of skin and internal organs. *Cancer 6* 347 (1953).
9 Hueper W C. *Occupatio al Tumors and Allied Diseases.* C C Thomas, Springfield, Ill 1942.
10 Binkley G W and Johnson H H Keratoacanthoma (mol luscum sebaceum) *A M.A Arch Dermatol 71* 66 (1955).
11 Ereaux, L. P Schopflocher P and Fournier C. J Kerato-acanthoma *A M A Arcl Derm tol., 71* 73 (1955)
1_ Farrell, H J Cutaneous melanomas w th special reference to prognosis. *Arch Dermatol and Syphilol., _6* 110 (1932).
13 Affleck, D H Melanomas. *Am. J Cancer ?7* 120 (1936).
14 Broders, A. C., and MacCarty W C. Melanoepithelioma. *Surg Gynecol and Obstet 23* 28 (1916).
15 Traub, E. F and Kell H The Common Mole. Its clinico-pathologic relations and the question of malignant degenera tion. *Arch Dermatol nd Syph ilol 41* 14 (1940)
16. Daland, E. M and H lmes, J A M lignant Melanoma Clin cal study N *Engl J Med 220* 651 (1939).
17 Becker W S. Pitfalls in the diagnosis and treatment of mela noma. *A I De m tol and Syph I I 69* 11 (1951).
18 Butterworth, T d Klauder J V Maligna t melanomas aris ng n moles. *J Am Med Assoc 10?* 759 (1931).
19. Muelling R J M lignant melanoma A omparative st dy of the inciden n the Negro ra *M I I ry Surgeon 103* 359 (1948).
?0 V n Scott, E. J Reinertson, R. I nd McCall C. B Prev alen histological types, and significance of palmar d planta nev *Can er 10*-363 (1937)

21 Klauder J V and Beerman, H Melanotic freckle (Hutchinson) Mélanose circonscrite précancéreuse (Dubreuilh) *A M A Arch Dermatol 71.2* (1935).
22 Allen A. C. and Spitz, S. Histogenesis and clinicopathologic correlations of nevi and malignant melanomas. Current status. *Arch Dermatol and Syphilol., 69* 150 (19.1)
23 Dorsey C. S. and Montgomery H *Blue nevus and its distinction from Mongolian spot and the nevus of Ota. J Invest Dermatol 2.* 22. (1954)
24 Brandt, G Melanoma of the skin with special reference to histological differential diagnosis, clinical picture, and end results of treatment. *Ann Chir et Gynaecol. Fenniae 45 (Suppl 3)*:1 (1956)
25 Dorn, H F Illness from cancer in the United States. *Pub l Health Repts U S 59* 33–43 6.–7 97–11 (1911)
26 Snapp R H Niederman D J and Rothman, S Experiments on the theory of photochemical formation of carcinogen from skin fats. *Cancer Research 10* 73 (1950).
27 Blum H F Review Sunlight as a causal factor in cancer of the skin of man. *J Natl Cancer Inst 9* 247 (1948).
28 Blum H F Sunlight and cancer of the skin. *J Natl Cancer Inst 1* 397 (1940)
29 Macklein M I Xeroderma pigmentosum. An inherited disease due to recessive determiners. *Arch Dermatol and Syphilol 34* 656 (1936)
30 Anderson N P and Anderson, H L. Development of basal cell epithelioma as a consequence of radiodermatitis. *Arch Dermatol and Syph 63* 586 (19 1)
31 Saunders, T S. and Montgomery H Chronic roentgen and radium dermatitis *J Am Med Assoc 110* 3 (1938).
32 Crosser Quoted in MacKee G M and Cipollaro A C *Cutaneous Cancer and Pre Cancer A practical monograph* American Journal of Cancer 1937
33 DeAlvis, C. Cutaneous carcinoma of the lower extremities. *Ann Surg 83* 663 (192)
34 Cory N A Frequency of syphilis with cancer of the lips, tongue and buccal mucous membrane *J Am Med Assoc* 5 8.8 (1920)
35 MacCormac H Discussion on the cancerous and precancerous conditions of the skin *Brit Med J* 157 (1921)
36 Love W R. and Montgomery H Epithelial cysts *Arch Dermatol and Syphil 4* 18 (1943)
37 Peden J C. Carcinoma developing in sebaceous cysts. *Ann Surg 1.8* 1136 (1948).

38. Treves, N and Pack, G T The development of cancer in burn scars. An analysis and report of thirty-four cases. *Surg Gynecol Obstet., 51* 749 (1930)
39 Lawrence, E. A. Carcinoma arising in the scars of thermal burns, with special reference to the nfluence of the age at burn on the length of induction period. *Surg Gynecol. Obstet 95* 579 (1952)
40 Montgomery H and Waisman, M Epithelioma attributable to arsenic. *J Invest Dermatol 4* 365 (1941)
41 McDaniel W E., and Mason, L. M Malignant dyskeratosis, erythroplasia of Queyrat type. *Arch Dermatol. and Syphilol 60* 419 (1949)
42. Steiner P E. Evaluation of the cancer problem. *Cancer Re searcl 12* 455 (1952)
43 Lattes, R., and Kessler R. W Metastasizing basal-cell epithelioma of the skin Report of two cases. *Cancer 4* 866 (1951)
44 Montgomery H. Precancerous dermatosis and epithelioma in situ. *Arcl Dermatol and Sypl lol 39* 387 (1939)
45 Warren, S and Hoerr S. O A study of pathologically verified epidermoid carcinoma of the skin. *Surg Gynecol. Obstet., 69* 726 (1939)
46. Ackerman L. V and del Regato J A. *Cancer Diagnosis Treatment nd Prognosis.* C. V Mosby Co., St. Louis, Mo., 1951.
47 Editorial. Cancerous melanoma. *J Am Med Assoc 139* 1151 (1949).
48 Dargeon H W E ersole J W and Del Luca, V Malignant melanoma in an infant. *Cancer 3* 299 (1950).
49 Holland, E. A case of transplacental metastasis of malignant melanoma from mother to fetus. *J Obstet and Gynaecol. Brit Empi e 56* 5 1 (1949).
50 Allen, A. C., and Spitz, S. Malignant melanoma. *Cancer 6* 1 (1953).
51 Pack, G T Perzik, S. L., nd Scharnagel I M The treatment of malignant melanoma—report f 862 cases. *Cal f Med 66* 283 (1947)
5_ Pack, C T nd Scharnagel, I M The prognosis for malignant melanoma in the pregnant woman *Ca er 4* 5 1 (1951)
53 Spitz, S. Melanomas n childhood. *Am J P th 4*.591 (1948)
54 M Whorter H E and Woolner L B Pigmented nevi juvenile melanomas nd m lignant melanomas in hildren *Cancer* 561 (1951)
55 Stegmaier O C. nd Montgomery H Histopathologic studies

of pigmented nevi in children *J Invest Dermatol* ?0 51 (1953).

56 West, J P and Nickel, W F Paget s disease of the nipple *Ann Surg* *116* 19 (194?).

57 Plachta A and Speer F D Apocrine gland adenocarcinoma and extramammary Paget s disease of the vulva Review of the literature and report of a case. *Cancer* *7* 910 (1951)

58 Dockerty M B and Pratt J H Extramammary Paget s disease A report of four cases in which certain features of histogenesis were exhibited. *Cancer* *5* 1161 (195).

59 Wallace, H J and Whimster I W Vulval atrophy and leukoplakia *Brit J Dermatol* *63* ?11 (1951)

60 Sachs, W and Sachs, P Erythroplasia of Queyrat *Arch Dermatol and Syphilol* *58* 181 (1918)

61 Zoon J J Balanoposthite chronique circonscrite benigne à plasmocytes (contraérythroplasie de Queyrat) *Dermatologica* *105* 1 (19 ?).

6? Pillsbury D M Blank, H and Madden D J Low voltage x ray therapy in diseases of the skin *Arch Dermat l and Syph l l* 0 16 (1951).

63 Lehmann C F and Pipkin J L Radium in malignant cutaneous d sease *J Am Med Assoc* *15?* 1 (19 1).

64 Osborne E D Treatment of malignant cutaneous lesions. *J Am M d Assoc* *15?* 1 (19 1)

65 Mohs, F E Chemosurgical treatment of cancer of the face microscopically controlled method of excision *Arch Derm tol d Syph l l* 56 143 (1947).

66 M lkinson F D a d Rothman S Skin cancer it c uses, prevention and treatment *Ca* *7* 190 (19 7)

67 Andrews, C C., Domonkos, A M and Hurlbut W B Roentgen irradiation n the tre tment of epithelioma *J Am Med Assoc* *15?* ?1 (19 1).

68. Schreiner B F and Christy C J Results of irradiation treatment of c ncer of the lip Analysis of 63? cases from 19?? 1936 *R diology* *39* 293 (194?)

69 Lamb J H and Eastland, W E Cancer of the lower lip Treatment with radiation *J Am Med Assoc* *1?* 600 (1911)

?0 Eckert C T and Petry J L Carcinoma of the lip, *Surg Cl n No th Am* *?* 10?1 (1911).

71 Figi F A Epith lioma of the l wer lip S g Gyn ol Obstet *5?* 810 (1931)

7? Modlin J Neck dissection i cancer of the lower lip *Surgery* *?* 101 (1950).

?3 Taylor C W and Nathanson I T *Lymph Nod Metastases* Oxford Uni ersity Press, New York 194_

74. Staley C. J Unpublished observations, 1953 Ellis Fischel State Cancer Hospital. Columbia Mo Quoted by Ackermann and del Regato (46).
75. Clarke J M Mal gnant n elanomas s me points in treatment and prognosis. Australian New Zealand J Surg 22 8 (1952)
76. Pack, G T and Livingston E. M Treatment of Cancer and Allied Diseases Vol III Paul B. Hoeber New York, 1940
77 Fanger H., and Roberts, W F Malignant melanoma. A clinico-pathological study New Engl J Med 246 813 (1952)
78. Galgano, A. R. Long survival in malignant melanoma Report of a case. J Am Med Assoc., 152.518 (1953)
79 Pack, G T Scharnagel, I. M and Hillyer R. A. Multiple primary melanoma Report of 16 cases. Cancer 5 1110 (1952)
80. Meyer H W nd Gumport S. L. Malignant melanoma. Appraisal of the disease and analysis of 105 cases. Ann Surg 138 643 (1953)

Discussion

Question Does pregnancy change nevi? And if it does, does it alter the criteria for their management?

Dr. Malkinson D ring the pregnant state, new pigmented lesions may be found on the skin surface. Some of these perhaps are junction nevi. Some of them have been called lentigines. Preexisting pigmented lesions may grow more rapidly or may enlarge progressively whereas before pregnancy their size was static. As a rule melanoma also grows much more rapidly during pregnancy than it does in the non-pregnant state nd metastases occur much more readily I think, then, that some enlargement in size may be expected in certain benign pigmented lesions in the pregnant patient. One has to watch these carefully and if other changes become apparent such as I described previo sly—crusting, bleeding, ery rapid enlargement and so on—these lesions should be excised.

Dr. Pinkus I want to report that one of our res dents, working for his master s thesis, surveyed the treatment results that the average dermatologist in his office gets in carcinoma of the skin. Now the University of Chi ago the center Most of the publications n this field have come fro large centers where of course treatment is much more routine nd equalized. But we talk about material in onnection with 250 cases coming from the offices of five dermatologists in Detroit, one of them my own, with different men preferring different methods. Some preferred x-ray treatment, others curettage, surgery or electrocautery Everyone of them probably used all of

these modalities in some cases. There was an overall five year cure rate of about 91% in these cases and it varied only by 1 or 2% up or down for either x ray surgery or curettage. I would like to draw two conclusions. In the first place, the dermatologist in practice is quite qualified and successful in treating cancer of the skin which you all know has been sometimes doubted. *And in the second place* whatever the experienced dermatologist uses in his office to treat skin cancer apparently has quite a high and satisfactory rate of cure

DR. SULZBERGER *I would like to say one thing in order to avoid* any misinterpretation of what was said previously about the carcinogenic effects of tar Coal tar as used therapeutically is not carcinogenic We have looked and searched and asked in order to try to find cases in which coal tar or any of the coal tar derivatives used in topical *application have produced carcinomas. The only* case we could find was one which was questionable. That was a man who had applied liquor carbonis detergens for pruritus ani through many years and then *had* developed a carcinoma of that area We couldn t tell from the report if it was in the rectum or on the skin Certainly coal tar is not a carcinogen as used therapeutically

I would like to ask Dr Malkinson if he has heard of dermabrasion for the treatment of senile skin or photodamaged skin as recom*mended by Dr Erwin Epstein He believes that this is the principal* indication for dermabrasion or plastic planing today and that in people with senile skin keratoses, telangiectases, pigmentations and depigmentations dermal rasion *produces a soft pliable skin He* thinks it is because the regeneration comes from beneath, where the cell were not exposed to the damaging effects of the light and other elements, and therefore they grow new cell on the surface which have another twenty or thirty years to go

DR. MALKINSON I was aware of Dr Epstein s report in the *Archives of Dermatology* and certainly this method deserves further investigation In a way it is quite analogou to the mucous membrane operation *which I described for leukoplakia of the lower lip. The* decisive factor determining the potential success of planing as a prophylactic measure against carcinoma in farmer skin depends, of course on what the site of the carcinogenic effect of ultraviolet light is If this is relatively superficial formation of a new line of epidermal cells from adnexal structures together with formation of some new connective tissue has drastically reduce the skin s susceptibility to sunlight induced changes and carcinoma again for many years On *the other hand if planing simply restores the skin from a cosmetic* viewpoint without altering the previously induced carcinogenic factors, then there will be no change in the incidence of skin cancers. Obviously time alone will tell u what the effectiveness *of the planing* procedure is in such patients.

INDEX